SKILL ACQUISITION IN PEOPLE WITH CHRONIC UPPER LIMB SPASTICITY AFTER STROKE

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ABSTRACT

Background

After a stroke, a considerable proportion of people experience upper limb (UL) impairments, which may affect their activities of daily living. Focal spasticity is common, for which botulinum toxin-type A (BTX-A) is used increasingly. However, published randomised controlled trials have not used valid outcome measures to assess the effects of BTX-A on spasticity and have hardly explored its impact on UL function. The primary aim of this thesis was to investigate whether task-specific UL practice in the form of an evidence-based, functional skill acquisition programme, administered after BTX-A, would have any differential effects on upper limb spasticity or functional UL activity in people more than six months after stroke. The prerequisites were to: 1) clarify the definition of "spasticity", 2) pilot a novel biomechanical spasticity measurement device, 3) standardise the assessment of arm function, 4) systematically review the literature on the effects of BTX-A and 5) compile an evidence- and theory-based skill acquisition programme.

Methods

Design: randomised controlled feasibility study with four repeated measures and a blinded assessor. Fourteen participants (time after stroke: range 1.4 -11.0 years) gave informed consent and were randomised into either the experimental group (EG: BTX-A plus skill acquisition) or the placebo control group (CG: BTX-A plus inflatable arm splint). Outcome measures were: Action Research Arm Test, Canadian Occupational Performance Measure, grip force of the affected hand, Stroke Impact Scale, EMG of the elbow flexors, biomechanically measured resistance to passive movement and Ashworth scale. Outcomes were assessed at baseline and weeks 4, 7 and 13 following BTX-A injection. Differences in change between the two groups were analysed using the Mann-Whitney U-test. Applying the Bonferroni correction for three repeated measures yielded a critical p-value of 0.017.

Results

At baseline, there were no significant differences between the two groups in any of the dependent variables. Compared to the CG, the EG improved in self-reported hand function between baseline and week 4 (median change 25%, range 0 to 30% vs. CG: median change 0%, range -10 to 0%; p=0.04). The EG also improved in arm function between baseline and week 7 (median ARAT change 4 points, range 1 to 8 points vs. CG: median change -1 point, range -3 to 0 points; p=0.003) as well as in self-reported ADL between baseline and week 13 (median change 11.3%, range 5 to 20% vs. CG: median change 0%, range -2.5 to 5%; p=0.02). Only the differential improvement in ARAT by the EG reached statistical significance. There were no significant differences between the two groups in any of the other outcome measures. Although the programme was perceived as intensive, most participants in the experimental group had found the intervention to be enjoyable.

Conclusion

The main finding of this study was that people with severe and chronic upper limb spasticity may still improve in functional activity involving their affected arm, using a combination of BTX-A and a functional skill acquisition programme - without exacerbating spasticity. BTX-A alone did not improve upper limb activity in this study. Implications for clinical practice and research were discussed.

PROLOGUE

The seed for this thesis was sown when I was a student in physiotherapy. I remember asking one of the lecturers how "practice makes perfect". The answer rang loud and clear: a look as if I had asked whether the Pope was catholic. The question has haunted me ever since.
Experience with professional dancers – masters in skill acquisition – further fuelled my interest. It was when I continued to study at the Faculty of Human Movement Sciences in Amsterdam that I learned about the theories and the evidence I had been searching for. It was an exciting time.

Several years later, turning my eyes to those having to relearn functional skills following a brain lesion, I was surprised to find that little of the research relating to skill acquisition had been incorporated within neurological rehabilitation. The domain of re-learning functional skills by people with a lesion of the central nervous system constituted – and still does – largely uncharted terrain.

The focus of this thesis is on re-learning activities of daily living that involve the affected arm by people who are in the chronic stage after a stroke. The wish is that it may contribute a piece – albeit a very modest one - to the map of this terrain. The hope is also that this thesis may encourage clinical colleagues to continue to challenge both themselves – as well as their patients – to continue to learn.

ACKNOWLEDGEMENTS

This thesis is the result of a journey, which was guided and accompanied by several distinguished companions, with whom it was both a privilege and a great joy to work. In the following section, I would like to acknowledge their input and express my gratitude to them.

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In terms of funding, I am very grateful to Action Research for providing a continuous source of financial support to CREST, without which this thesis, and indeed many other projects at CREST, would not have been possible. I would also like to thank Allergan Ltd., High Wycombe, UK, for providing an unrestricted educational grant to one of the studies, as well as Ipsen Ltd., Slough, UK, for their financial support to Hunters Moor Regional Neurological Rehabilitation Centre in Newcastle upon Tyne,

which helped to secure physiotherapy input into the main study in the early stage of its development.

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I am also very grateful to my colleagues in the SPASM consortium (Support Programme for Assembly of Database for Spasticity Measurement), for teaching me so much about their own fields. This programme was funded through the European Commission (Thematic Network Programme QLTR 2000-00818). Part of the literature review, which focuses on biomechanical methods for the measurement of spasticity, is based on a component of work of the SPASM project, which was led by Prof. Iain Swain and Dr. Duncan Wood in Salisbury, UK. The development of a definition of spasticity was a SPASM-team effort. Hosting the SPASM conference in December 2004 with the whole group was a particular privilege and a wonderful experience. I would like to thank the members of both EU consortia for stimulating debates as well as good fun during our numerous meetings. May the good work continue!

After two years at CREST, the project continued at Queen Margaret University College, Edinburgh. Dr. Julie Hooper became Director of Studies, with whom I spent countless enjoyable hours, discussing the therapeutic programme for the main study. Her clinical experience was crucial, while her continuing encouragement and warm sense of humour were instrumental in getting the project through a challenging stage. Following Julie's departure from QMUC, Prof. Marie Donaghy took over and I am indebted to her for her enthusiasm, guidance and continuing encouragement - particularly for exploring the topic of mental practice, on which we had several fruitful discussions. Dr. Lisa Salisbury joined the team when the thesis was taking shape and I would like to thank her for her commitment,

encouragement and clarity at a time when snow blindness was setting in. One of the sections of the literature review on physiotherapy after stroke is partially based on a book chapter written with Gillian Baer at QMUC, whom I thank for her comments on the sections on Bobath and the Motor Relearning Programme and some of the material on Constraint Induced Therapy.

The main ideas for this thesis were based on questions that people attending the Spasticity Outpatient Clinic at Hunters Moor Regional Neurological Rehabilitation Centre in Newcastle upon Tyne put to us. I am indebted to all the participants in the studies, for their selfless generosity, curiosity, commitment, patience and sense of humour, which they brought to the projects. This thesis is really dedicated to them, as without their input, this work could not have been completed. Working with the participants was doubtlessly the most enjoyable and enlightening part of the journey. It also emphasised how much more research is required, in order to improve rehabilitation after stroke.

"Hunters Moor" provided the clinical base for the work and was invaluable for shaping ideas and developing protocols. I am particularly indebted to Sandra Stark MSc. MCSP, whose foresight, commitment to research and input were all invaluable. Thanks to her resourcefulness, it was possible for Julia Mackenzie MCSP to join the main study. Julia was soon to become my right hand, as without her expertise, invaluable ideas regarding patient-centred outcome assessment, endless patience and companionship, this study could not have taken place. The fact that Julia managed to achieve such high attendance figures, particularly in the control group, pays tribute to her excellent clinical and interpersonal skills (and in addition, I suspect, her superior entertainment skills).

Additionally, I am most grateful to the physiotherapists and occupational therapists at Hunters Moor for giving their views during pilot work, numerous in-service sessions and presentations of preliminary findings.

The experimental studies could not have happened without a committed Outpatient Spasticity Clinic Team at Hunters Moor. I am particularly grateful to Lesley Kidd, operational and clinical lead for Out-Patients, for her enthusiasm, fine sense of humour, commitment and willingness to go the extra mile to enthuse patients for the studies. Without the support from Dr. Philippe Vuadens, Dr. Angus Graham, Dr. Laura Graham, Dr. Zacc Falope, Dr. Ashish Macadden, Dr. Paul Weeks, Dr. Âine

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Finally, and most importantly, I am infinitely grateful to my partner Chris Eilbeck, who has managed to live with me throughout this project. Not only did he compile the computer programmes that were used for various randomisation procedures in the main study, but moreover, he kept me going, day by day – sometimes by tearing me away from my work to join him going up a mountain. In particular, I am grateful to Chris for enveloping me in his characteristically endless calm, love and Zen-like wit - and for reminding me that this thesis is only just the beginning...

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CHAPTER ONE

LITERATURE REVIEW

1.1 INTRODUCTION

1.1.1 THE IMPACT OF STROKE

Stroke is defined by the World Health Organisation (WHO) as:

> *"an acute neurologic dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain* (WHO, Stroke-1989; 20: p. 1412).

Stroke is the third leading cause of death in developed countries and was responsible for 10% (i.e. 5.5 million) of all deaths in 2002 worldwide (Mackay and Mensah, 2004). Stroke is also the leading cause of healthy years lost in later adulthood (Kalache and Aboderin, 1995) and the most important cause of disability among adults (Khaw, 1996). Although stroke-related mortality trends showed a decline over the period from 1965 to 1998 in some developed countries (Levi *et al.*, 2002), the number of chronic stroke patients in the community at a global level is predicted to increase (Truelsen et al., 1997; Mackay and Mensah, 2004). This will place a growing burden on carers, families, health and social services (Malmgren *et al.*, 1989; Mackay and Mensah, 2004). In terms of cost, stroke is associated with a vast economic burden (Palmer *et al.*, 2005), with the UK spending 4% of its National Health Service budget on stroke care (Rudd *et al.*, 2000).

Following a stroke, approximately one third of patients will die within the first month, one third will gain a good recovery, while the remaining third will be left with

considerable disabilities (Barnes and Ward, 2000). Stroke sequelae include a wide range of impairments[1], activity limitations[2] and participation restrictions[3], including difficulties with sensation and perception, executive functioning, cognition, upper and lower limb function (including mobility), bowel and bladder function, sexual function and relationships, orofacial function and communication, mood, vocation, leisure and social functioning. For comprehensive texts on these issues see Barnes and Ward (2000), Carr and Shepherd (2003), Barnes *et al.*, (2005), Edwards (2002), Stokes (2004). Each of these problems may have far-reaching implications for the well-being, autonomy, social integration and employment opportunities of those who survived a stroke and their families.

Problems affecting the upper limb after stroke are particularly common, often persistent and disabling (Parker *et al.*, 1986; Broeks *et al.*, 1999; Lai *et al.*, 2002). In an important study, Wyller *et al.* (1997) concluded that arm motor impairment[4], was the single most influential factor in determining the level of well-being one year after stroke, which in their cohort of stroke patients was lower than in a group of cancer patients with severe symptoms after treatment. The following sections will explore the impact of a stroke on upper limb function in more depth.

1.1.2 EFFECTS OF STROKE ON UPPER LIMB FUNCTION

1.1.2.1 Impairments affecting the upper limb

Commonly reported impairments after stroke include paresis (e.g. Parker *et al.*, 1986; Boissy *et al.*, 1999; Bourbonnais *et al.*, 2002; Turton and Butler, 2004),

[1] "Impairments" are defined as: "*problems in body function or structure such as a significant deviation or loss*" (World Health Organisation International Classification of Functioning, Disability and Health, 2001: p. 10). "Body functions" are defined as "*the physiological functions of body systems (including psychological functions)*" and "body structures" are defined as "*anatomical parts of the body such as organs, limbs and their components*" (*ibid.*).

[2] "Activity" is defined as "*the execution of a task or action by an individual*" and "activity limitations" are defined as "*difficulties an individual may have in executing activities*" (*ibid.*).

[3] "Participation" is defined as "*involvement in a life situation*" and "participation restrictions" are defined as "*problems an individual may experience in life situations*" (*ibid.*)

[4] Impairments and activity limitations are not restricted to the contralateral upper limb; several studies have shown that the ipsilateral arm may also be affected (e.g. Debaere *et al.*, 2001).

abnormal force production (Dewald *et al.*, 1995; 2001; Lum *et al.*, 1999), inappropriate muscle co-activation (Gowland *et al.*,1992; Kamper *et al.*,2003; Dewald *et al.*,2001; Eder *et al.*,2004), abnormal synergies (Sawner and LaVigne, 1992; Bobath, 1971; Archambault *et al.*,1999), difficulties with selective movements (Fugl-Meyer *et al.*, 1975; DeSouza *et al.*, 1980; Page 2000), loss of active and passive range of movement (Powell *et al.*, 1999), impaired sensation (Parker *et al.*, 1986), proprioception (Carey *et al.*, 1996) and pain, as well as contractures and deformities (Smith, 2004). Using motion analysis instrumentation, a number of studies reported reduced speed, increased movement variability and segmentation, as well as abnormal inter-joint coordination during pointing (Levin, 1996; Archambault *et al.*, 1999; Levin *et al.*, 2000), multi-peaked hand velocity profiles and compensatory trunk movements during reaching (van Vliet., 1993; Thielman *et al.*, 2004) and increased coupling between both upper extremities during bimanual activities (Rice and Newell, 2004).

Spasticity[5] is a particularly common impairment after stroke (Barnes, 2001; Edwards, 2002; Gray *et al.*, 1990; Levin and Feldman 1994; Levin *et al.*, 2000). Sommerfeld *et al.* (2004) estimated that 19% of stroke patients develop spasticity during the first three months after the acute event, while Watkins *et al.* (2002) reported that 38% of their sample developed spasticity in the first year. Especially when spasticity involves the upper limb, it may cause pain and interfere with the patient's self-care and ability to carry out activities of daily living (Barnes, 2001). These are indicators that some form of spasticity management may be required (Barnes, 2001) and Barnes *et al.*, 2001) estimated that approximately 20% of patients need intervention to reduce spasticity after stroke.

1.1.2.2 Activity limitations affecting the upper limb

Between 20% (Parker *et al.*, 1986) and 79% (Nakayama *et al.*, 1994) of stroke survivors regain full upper limb function at three months after the acute event, depending on their initial level of impairment (Nakayama *et al.*, 1994). Difficulties with functional activities involving the affected arm are common (e.g. De Souza *et al.*,

[5] The term "spasticity" is derived from the Greek σπαστικοσ, meaning "to tug or draw" (Sheean, 1998, p. 7).

1980; Wade *et al.*, 1983; Parker *et al.*, 1986; Heller *et al.*, 1987; Taub *et al.*, 1993; van der Lee *et al.*, 1999; Lai *et al.*, 2002) as well as problems with dexterity (e.g. Parker *et al.*, 1986; Heller *et al.*, 1987; Eder *et al.*, 2004). Forty-seven percent of stroke patients who were not admitted to hospital had severe arm impairments and considerable problems with instrumental activities of daily living (ADL) at one month after stroke onset (Lincoln *et al.*, 1998) and these problems remained virtually unchanged at one year (Lincoln *et al.*, 2000). Of those with limited arm function early after stroke, 50% still experienced considerable problems four years later (Broeks *et al.*, 1999). Difficulties with daily activities are persistent, as documented by Dekker *et al.* (1995) in their follow-up of stroke patients 5 years after discharge from rehabilitation.

In conclusion, problems affecting the arm after stroke are common, often severe and may have a detrimental impact on the person's every day function and well being. Before exploring the effects of different rehabilitation strategies aimed at improving arm function, it is important to understand its natural recovery after the acute event.

1.1.3 NATURAL RECOVERY OF ARM FUNCTION AFTER STROKE

Most studies detailing recovery of arm function after stroke reported that, in general, improvement is most rapid in the first three months after the acute event, although it may occur at a later stage in some cases (Wade *et al.*, 1983: Parker *et al.*, 1986; Heller *et al.*, 1987). Nakayama *et al.* (1994) followed 421 stroke patients on a weekly basis during their stay in hospital and found that significant recovery of arm function occurred only within the first four weeks.

At first glance, these studies suggest that recovery of arm function mainly takes place in the first three months after stroke, after which it slows down to reach a plateau in most patients at about six months. Based on these data, rehabilitation input often terminates at six months after the acute event, in the expectation that the patient has reached a plateau (Bach-y-Rita, 2000; Page *et al.*, 2005). However, Duncan *et al.* (2000) raised the issue that the definition of "recovery" depends on the tool used to measure it. For example, on the basis of the Barthel Index with a cut-off score of 90 points, 57% of patients in their cohort were deemed to have recovered

fully, but when they used the Fugl-Meyer test (Fugl-Meyer *et al.*, 1975) instead, this figure dropped to 37%. This discrepancy may be explained by the fact that the Fugl-Meyer test specifically assesses the affected side, is more impairment-orientated, has more test items and is more sensitive than the Barthel Index. The high percentage of patients obtaining full arm function in the study by Nakayama *et al.* (1994) may thus be explained by the choice of tools, which was restricted to two items of the Barthel Index together with selected items from the Scandinavian Stroke Scale. The Barthel Index items, however, comprise activities that may easily be managed without involving the affected upper limb and the authors may therefore have documented successful *compensation* rather than actual *recovery*. Studies using more specific, varied and sensitive outcome measures showed that although most recovery did take place within the first few months after stroke, there was also considerable variation between patients; improvements started later in some patients or continued over a longer period of time (Fugl-Meyer *et al.*, 1975; De Souza *et al.*, 1980; Parker *et al.*, 1986; Heller *et al.*, 1987; Broeks *et al.*, 1999). In other words, there is some evidence to show that upper limb function may still recover well past the traditionally assumed, three-month window and this questions the assumption that patients have reached their full rehabilitation potential at this point.

One question that also needs to be raised is whether enough input was provided for the affected arm in the early stage after the acute event. It has been reported that patients often feel that therapy in the initial stage after stroke emphasised balance and mobility and that insufficient attention was paid to their affected arm (Wade, 1997). The breakdown of therapy input in stroke units and general medical wards by Kalra *et al.* (1993) supports this impression. The relative neglect of the affected arm may have serious long-term effects, since according to Luria (cited in Levin and Grafman 2000, p. 367):

> *"automatic and instinctive reorganizations after a lesion simply exclude the dysfunctional part of the body".*

Difficulty in using the affected limb may lead to so-called "learned non-use" (Taub and Uswatte, 2003). Indeed, data from a study by Page *et al.* (2005) clearly showed that their group of stroke patients made virtually no use of their affected arm - despite reasonable scores on an arm function test. This interesting finding suggests that there may be some untapped potential that is masked by learned non-use. This

raises the question whether further rehabilitation in the chronic stage after stroke could still be instrumental in enhancing functional activity in the affected arm.

1.1.4 EFFECTS OF LATE REHABILITATION ON ARM FUNCTION

A small number of studies have shown benefits of upper limb rehabilitation that was provided well after the acute event (e.g. Taub *et al.*, 1993, 1998; Werner and Kessler, 1996; van der Lee *et al.*, 1999; Kunkel *et al.*, 1999; Luft *et al.*, 2004; Page *et al.*, 2005). Ground-breaking neuroimaging studies with people in the chronic stage after stroke have also shown that improvements in arm function following specific treatment were associated with structural and functional neuroplastic changes in the brain (Nelles *et al.*, 2001; Liepert *et al.*, 2001; Levy *et al.*, 2001). It is now accepted that, even in adult humans, neurogenesis may occur at least in the hippocampus (Eriksson *et al.*, 1998) and that, in the chronic stage after a brain lesion, improvements may arise from increased neuronal activity (Bach-y-Rita, 2000). This important evidence suggests two things: first, rehabilitation should *continue* in the chronic stage after stroke. Second, plasticity needs to be driven by *targeted* rehabilitation in order to obtain meaningful functional improvement. These two points will be further discussed in the following sections.

1.1.5 CLINICAL GUIDELINES FOR CONTINUING REHABILITATION AFTER STROKE

In relation to the first point in the previous section on continuing rehabilitation after stroke, a number of general guidelines and service frameworks have been developed in the UK to improve and standardise continuing care. The National Clinical Guidelines for Stroke in the UK (Royal College of Physicians, 2004) recommend that:

> "*any patient with disability after 6 months or later after stroke should be assessed for a period of further targeted rehabilitation to be given where appropriate*".

This guideline has also been included in the National Framework for Older People (NICE, 2001). Both the SIGN guidelines [www.sign.ac.uk/] and the Occupational Therapy Concise Guide for Stroke (NANOT, 2002) include the recommendation to

provide opportunities for people who have had a stroke to review their long term rehabilitation needs. On the basis of the National Clinical Guidelines for Stroke, the Chartered Society of Physiotherapy in the UK has formulated physiotherapy-specific guidelines (2002), which stipulate that treatment should be meaningful and functionally relevant and these principles are also endorsed by the National Association of Neurological Occupational Therapists (NANOT) in the UK. Thus, clinicians involved in stroke rehabilitation are expected to provide treatment that is of the highest possible standard, provided at appropriate times at any stage after the acute event and that yields outcomes that are meaningful to the patient.

1.1.6 TARGETED UPPER LIMB REHABILITATION IN THE CHRONIC STAGE AFTER STROKE

1.1.6.1 Spasticity

Although reducing spasticity *per se* is rarely a treatment goal (Thompson, 1998; Barnes, 2001; Ward and Ko Ko, 2001), some form of intervention is usually required in cases where spasticity interferes with function, causes pain or where long-term complications are expected (Thompson, 1998; Barnes, 2001). The evidence for any form of physical management in the treatment of spasticity is inconclusive (SIGN Stroke Guideline 4.2.2)[6]. Pharmacological agents for treating spasticity may be systemic (e.g. oral Baclofen) or local (e.g. phenol or botulinum toxin[7], Ward and Ko Ko, 2001). However, systemic, oral anti-spastic medication may have unwanted side effects such as drowsiness and dyskinesia (Ward and Ko Ko, 2001). Therefore, in cases where spasticity is a local problem, focal pharmacological agents tend to be preferred. Botulinum toxin type-A (BTX-A) is used increasingly, as its effects have been shown to involve few side effects while its administration is relatively straightforward (Barnes, 1997; Hesse, 2000; Davis and Barnes, 2001). However, the methodology for evaluating the effects of BTX-A on spasticity has generally been lacking in rigour. This appears to be associated with the confusion in the literature, as well as in clinical practice, as to what "spasticity" is and how it should be assessed

[6] Scottish Intercollegiate Guidelines Network (SIGN): Guidelines on Stroke [www.sign.ac.uk/]

[7] Botulinum toxin is produced by the bacterium *Clostridium botulinum*.

(Sheean, 1998; Edwards, 2002). Additionally, evidence demonstrating the impact of BTX-A on functional activity of the arm in stroke was insufficient (van Kuijk *et al.*, 2002).

Clinical guidelines pertaining to the treatment of adult spasticity with botulinum toxin stipulate that it should be part of a comprehensive intervention programme:

> *"Botulinum toxin injection must be part of a rehabilitation programme involving post-injection exercise, muscle stretch and/or splinting to achieve an optimal beneficial clinical effect"* (Barnes *et al.*, 2001, p.3[8]).

This is based on the assumption that BTX-A reduces excessive muscle contraction and thereby creates a window of opportunity for achieving other treatment goals (e.g. Bhakta *et al.*, 1996; Sheean 1997; Hesse 2000, 2001; Bhakta 2000; Richardson and Thompson, 1999; Graham *et al.*, 2000). The guideline makes sense on the basis of sound clinical reasoning, but what is the evidence to support it? What is the efficacy of additional treatment together with BTX-A? Which therapeutic "package" is most effective for improving arm function in particular? It appears that research on the effects of different treatment "packages" including BTX-A is very limited. Specifically, at the time of writing, there was no published evidence on the differential effects of additional task-specific training when combined with BTX-A, which the literature indicated could be an important factor in cases where the aim is to improve function.

1.1.6.2 Activity limitations

The key ingredient that emerges from systematic reviews on stroke rehabilitation as instrumental in enhancing functional recovery is task-specific training (van Peppen *et al.*, 2004; Steultjens *et al.*, 2003). This involves training the specific skills one is aiming to improve. The evidence supporting task-specific training for restoring balance and gait is strong and so is the evidence supporting Constraint Induced Therapy for improving arm function (van Peppen *et al.*, 2004). However, Constraint Induced Therapy is only suitable for patients with at least some degree of active wrist

[8] This guideline can also be found in the Guidelines for the use of botulinum toxin (BTX) in the management of spasticity in adults, issued by the Clinical Effectiveness and Evaluation Unit of the Royal College of Physicians (2002, p. 5).

movement, which excludes those who have been more severely affected. With regards to the more severely affected population, the research on the efficacy of rehabilitation strategies for improving upper limb function is limited and contradictory and clearly in need of further work.

1.1.7 AIMS OF THE THESIS

Given the prevalence, severity, persistence and ecological impact (i.e. the effects on a person's every day life) of spasticity and activity limitations involving the upper limb after stroke, together with the emerging evidence that rehabilitation in the chronic stage after stroke may still be beneficial to improve arm function and the possibility to create a window of opportunity through botulinum toxin in those with spasticity, the key research question of this thesis was: *how may functional activity of the affected arm be enhanced in people with chronic spasticity after stroke*?

More specifically, the primary aim of this thesis was to explore the differential effects of additional task-specific upper limb training in the form of a theory- and evidence-based functional skill acquisition programme, provided together with botulinum toxin, on activity and spasticity involving the affected upper limb in a feasibility RCT with people in the chronic stage after stroke. One of the prerequisites for this study was to clarify the definition of "spasticity", which was a particular challenge, given that this impairment is notoriously enigmatic and therefore problematic to measure. The subsequent aims were to establish a valid and clinically relevant methodology for measuring spasticity and arm function, and finally to compile and evaluate the effects of a functional skill acquisition programme.

1.1.8 STRUCTURE OF THE THESIS

The previous sections set the scene for the thesis by identifying the nature, prevalence and severity of common upper limb impairments and activity limitations following stroke. The case was made for continuing rehabilitation for people in the chronic stage after stroke, having shown that arm function may recover over a longer period of time than what has been assumed traditionally, and by having provided evidence to support the efficacy of specific forms of interventions at that stage. From

the general stroke literature, task-specific training emerged as one of the most effective ingredients, but the body of literature pertaining to upper limb rehabilitation in the chronic stage after stroke is limited and contradictory. In order to inform the content and intensity of an evidence-based therapeutic programme, designed to improve functional activity of the affected UL in the chronic stage after stroke, a review of the literature was required. This comprises the following strands: -

The first strand (section 1.2) discusses the concept of spasticity. It argues that it is necessary to begin by defining this concept more clearly in order to be able to establish the efficacy of any spasticity management strategy. Next, a range of methods for measuring upper limb spasticity are critically appraised and recommendations are put forward for best practice in general and for subsequent pilot work in Chapter Two in particular. This review was carried out within the context of the EU SPASM Thematic Network[9], a multidisciplinary consortium including consultants in neurological rehabilitation, bioengineers, allied health professionals and movement scientists.

The second strand of the literature review (section 1.3) continues on the theme of spasticity and concentrates on the evidence pertaining to the treatment of focal spasticity by means of botulinum toxin Type-A (BTX-A), a pharmacological agent that is increasingly gaining acceptance throughout the world. A systematic review of the literature on the efficacy of BTX-A on UL spasticity and function after stroke reveals an important methodological flaw with regards to the assessment of spasticity, in addition to a dearth of research on the effects of BTX-A on arm function.

The next section (section 1.4) sets out to further explore the literature on BTX-A and shows that only a few studies have reported on the differential effects of additional treatment, when administered together with BTX-A. This indicates that there is little evidence to support the clinical guideline that, for optimum treatment effects, BTX-A should be provided alongside other forms of treatment as part of a comprehensive rehabilitation programme. At the time of writing, there were no publications

[9] Support Network for the Assembly of a Database for Spasticity Measurement QLTR 2000-00818, European Commission [http://www.ncl.ac.uk/spasm/]

investigating the differential effects of exercise or skill acquisition, when provided together with BTX-A.

The ensuing strand of the literature review (section 1.5) focuses on arm function after stroke by critically evaluating the evidence underpinning a range of commonly used therapeutic strategies. The discussion pertaining to the concept of task-specific practice reveals the strengths, but also the gaps and contradictions in the literature. Additionally, it underlines the dearth of evidence in the stroke literature pertaining to *how* task-specific training should be structured in order to achieve long-term carry-over into functional activity.

The issue of organising task-specific training in non-impaired populations is addressed in the next strand of the literature review (section 1.6), as it summarises the main findings from the general motor learning literature in terms of structuring practice and feedback. This section serves to inform the functional skill acquisition programme, which features in the feasibility RCT, detailed in Chapters Three to Five.

Finally, by synthesising research on BTX-A, neurological physiotherapy and skill acquisition in non-impaired populations, recommendations are put forward in section 1.7 to inform the content and intensity of the ensuing feasibility RCT.

In preparation of this RCT, pilot work was required to explore the properties of a novel spasticity measurement device that incorporated the recommendations from the literature review. The instrument was designed to quantify biomechanical and neurophysiological variables associated with spasticity. This pilot study is reported in Chapter Two. Calibration work supports the scientific properties of the individual components of the device when tested in laboratory conditions, but a number of methodological challenges, associated with the application of the device in the actual testing situation, are also identified. Given the alternatives for measuring spasticity however, it is argued that this device is the preferred method for measuring outcomes in the ensuing RCT.

Chapters Three to Five report the randomised, placebo-controlled feasibility study that aims to explore the differential effects of a functional skill acquisition programme

combined with BTX-A. This therapeutic programme is based on the evidence and theory discussed in the literature review. Chapter Three details the study aims, hypotheses and methodology. Chapter Four presents the results and Chapter Five critically discusses the findings, compares them with similar published work, highlights study limitations and sources of error and suggests avenues for future research and clinical practice.

Finally, Chapter Six aims to reach beyond the confines of this thesis by reflecting on broader issues in stroke rehabilitation. Recommendations for clinical practice, audit and further research in the field of stroke rehabilitation in general are put forward.

The structure of this thesis, and the research questions addressed in each chapter, is outlined in fig. 1.1

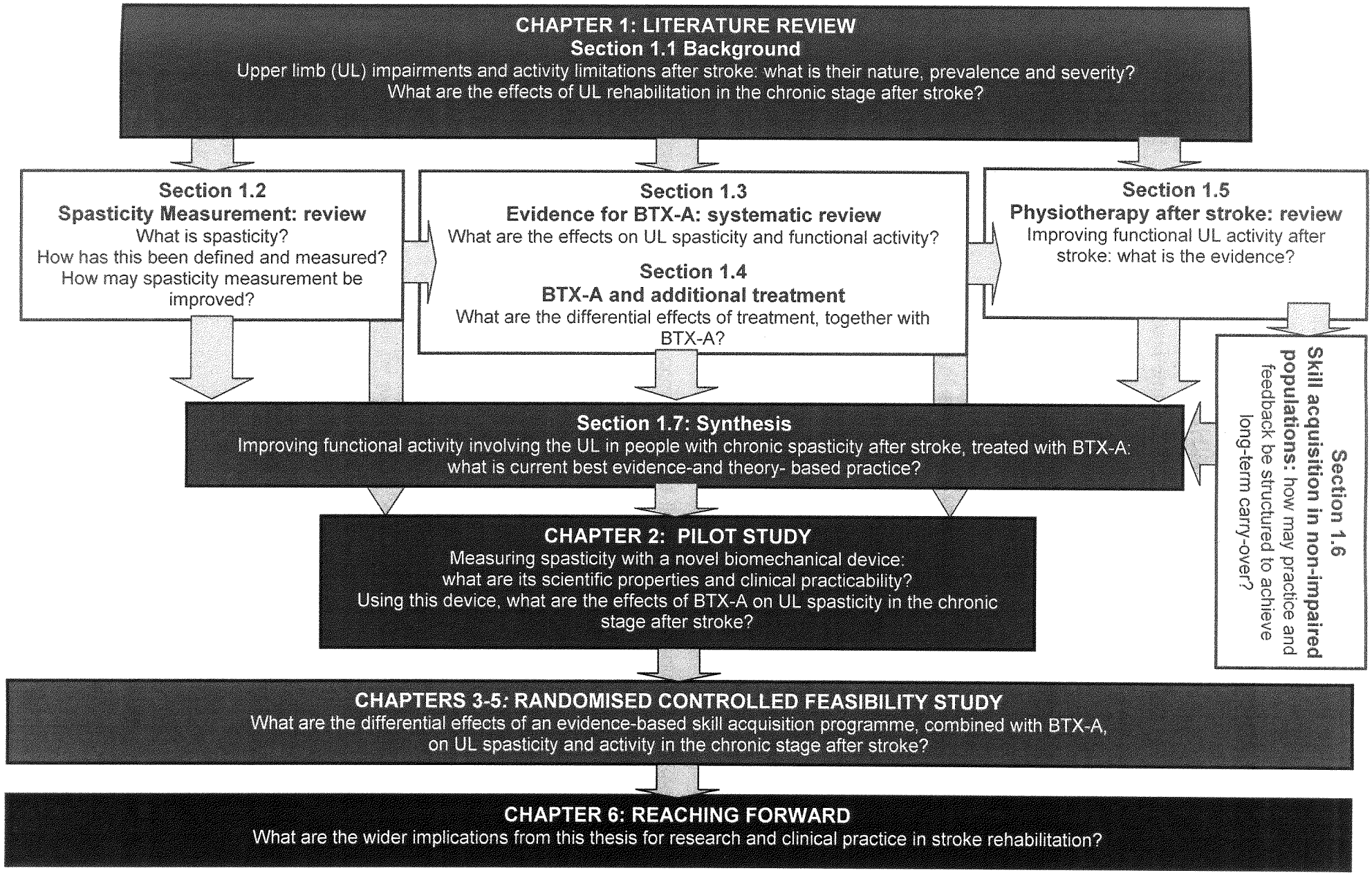


Fig. 1.1 Flow chart of the research questions addressed in this thesis
UL: upper limb, BTX-A: botulinum toxin-Type A

1.2 BIOMECHANICAL MEASUREMENT OF UPPER LIMB SPASTICITY: CATCHING THE ENIGMA

"Although spasticity is difficult to define, neurologists recognise spasticity when they see it – at least they think they do"

Young (1994)

1.2.1 INTRODUCTION: DEFINING SPASTICITY

1.2.1.1 Clinical relevance of assessing spasticity

As explained in the section 1.1.2, spasticity is a common problem following a lesion of the upper motor neuron (UMN), with approximately 38% of stroke patients developing this impairment in the first year after the acute event (Watkins 2002). Particularly when it involves the upper limb, spasticity may cause pain and interfere with the patient's self-care and ability to carry out activities of daily living (Barnes, 2001). This explains why approximately 20% of people are estimated to require treatment for spasticity after stroke (Barnes *et al.*, 2001).

Barnes (2001) published a comprehensive flow diagram for clinical decision making with respect to spasticity management, which shows that spasticity does not automatically require treatment. However, in those cases where it does need intervention, it is important that any effects can be determined accurately. This, in turn, requires a clear definition of the concept of spasticity, as well as accurate and reliable measurement tools.

Defining and measuring spasticity are the focus of the current section, which lays the foundations for Chapters Three to Five, where the effects of a specific spasticity management strategy will be explored. The current chapter was developed within the context of the EU Thematic Network SPASM[1].

[1] Support Network for the Assembly of a Database for Spasticity Measurement QLTR 2000-00818, European Commission [http://www.ncl.ac.uk/spasm/]

1.2.1.2 Defining spasticity

It is important to place the phenomenon of spasticity in the context of the UMN syndrome as a whole. This is a constellation of symptoms, which are traditionally divided into "positive" and "negative" phenomena (Barnes and Johnson, 2001). Positive symptoms are associated with an exaggeration of motor activity, whereas negative symptoms arise from a lack of it (Table 1.1). According to Sheean (1998), most of the positive symptoms of the UMN syndrome arise from exaggerated spinal reflexes[2], but their pathophysiology differs, as does their response to treatment. A full discussion of the positive symptoms other than spasticity can be found in Sheean (1998, 2001).

Table 1.1

Examples of "positive" and "negative" symptoms of the Upper Motor Neurone Syndrome

(based on Barnes, 2001: p.2)

Upper Motor Neuron Syndrome	
Positive features	**Negative features**
Spasticity Spastic dystonia Associated reaction Clasp-knife phenomenon Clonus Spasm Co-contraction Increased tendon reflexes Abnormal reflexes (e.g. Babinski)	Hypotonia Paresis Loss of dexterity Fatigueability

Probably the most commonly used description of spasticity is Lance's (1980):

> *"a motor disorder, characterised by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the upper motor neurone (UMN) syndrome"*

The crux of Lance's definition of spasticity is the stretch reflex. In clinical practice however, this concept often refers to the UMN syndrome in its entirety, rather than just one component of it (Edwards, 2002). This is reflected in the way in which

[2] Spinal reflexes may be subdivided into proprioceptive reflexes and cutaneous/ nociceptive reflexes. Spasticity is a proprioceptive reflex.

spasticity is commonly assessed in practice, i.e. by means of the (Modified) Ashworth scale (van Wijck *et al.;* 2001). Both the Ashworth Scale (Ashworth, 1964) and its modified version (Bohannon and Smith, 1987) yield an overall indication of resistance to passive movement (RTPM) encountered when the clinician briskly moves the patient's relaxed limb through its range of motion. However, it is important to note that several factors contribute to RTPM. These may be categorised as "neurogenic" or non-neurogenic (Katz and Rymer, 1989; Johnson, 2001). Figure 2.2 gives an overview of these two distinct contributions to RTPM, which will be further explained in the following sections.

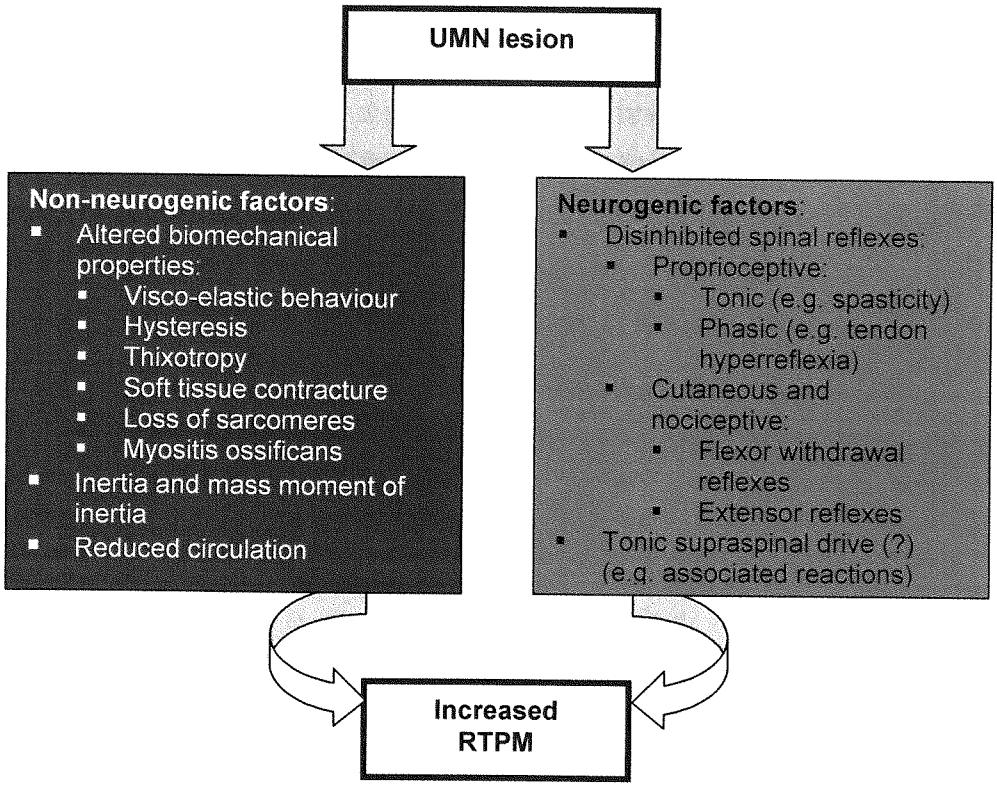


Figure 1.2
Resistance to Passive Movement (RTPM) following an UMN lesion: neurogenic and non-neurogenic factors
Based on Johnson (2001) and Sheean (1998).

1.2.1.3 Neurogenic contributions to resistance to passive movement (RTPM)

According to Lance, spasticity is an exaggeration of the tonic stretch reflex (Sheean, 1998). "Tonic" reflexes are those responding to a sustained elongation, e.g. elicited through the Ashworth test. In contrast, "phasic" reflexes are reactions to a fast perturbation, e.g. the tendon tap (Sheean, 1998). Details of the pathophysiology of the stretch reflex can be found in Sheean (1998).

Normally, there is a balance between inhibitory and excitatory influences from the brain stem upon the activity of spinal reflexes (fig. 1.3). Inhibition of spinal reflexes is mediated through the cortico-reticular fibres. These facilitate the ventromedial reticular formation in the medulla, which in turn inhibits the stretch reflex via the dorsal reticulospinal tract (DRT). Excitation of spinal reflexes is mediated through two pathways: the first originates from a diffuse brainstem area involving the basal diencephalon, tegmentum of the midbrain and pons and part of the bulbar reticular formation in the medulla and exerts its excitatory influence via the descending medial reticulospinal tract (MRT). The second pathway commences in the lateral vestibular nucleus in the medulla and exerts its influence via the descending lateral vestibulospinal tract (VST). After a lesion of the cortex or the internal capsule, the overall balance is tipped towards excitation, because the inhibitory influence of the DRT is diminished whilst the excitatory influence of the MRT and the VST is spared, as these systems are not under cortical control.

An important question is whether the hyperexcitability of the stretch reflex stems primarily from an *increased stretch reflex gain* or from a *lowered stretch reflex threshold* at which the stretch reflex is elicited[3]. The stretch reflex gain is the amount of force required to move the passive limb in proportion to the change in joint angle and the reflex threshold is the angular threshold at which the stretch reflex is elicited (Katz and Rymer, 1989). From their review on neurogenic and non-neurogenic factors contributing to RTPM, Katz and Rymer (1989) concluded that in spastic hypertonia, stretch reflex threshold but not reflex gain was the key

[3] Thilman *et al.* (1991, cited by Sheean, 2001, p. 26) suggested that spasticity represents a "*qualitatively new reflex*", since stretch reflexes do not occur in the relaxed muscles of non-impaired subjects unless very high velocities are used (i.e. 200 deg/s, or as high as 500 deg/s (Ashby and Burke (1971), cited in Sheean (1998)).

abnormality. As the ensuing literature will show, stretch reflex gain and threshold are commonly used parameters in the measurement of spasticity.

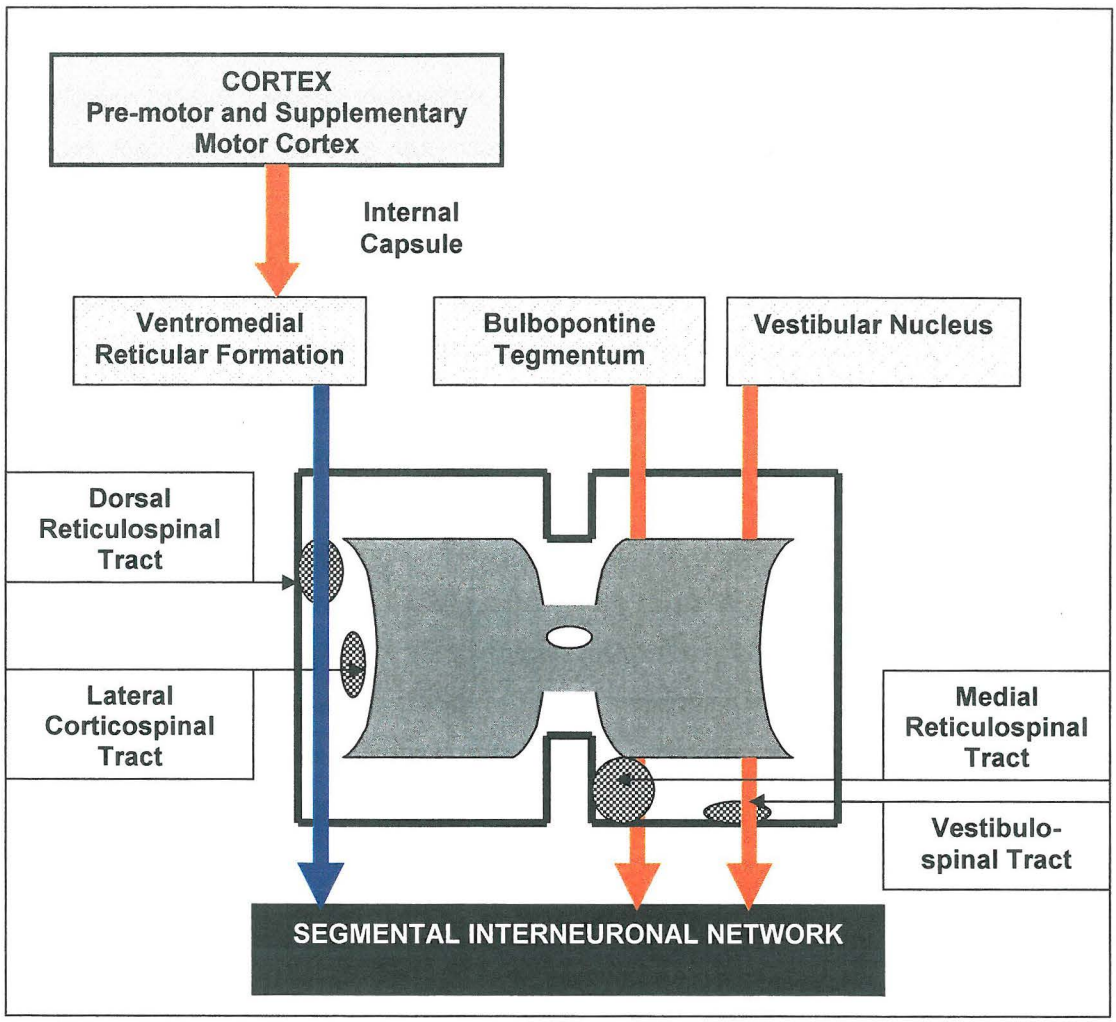


Figure 1.3
Schematic overview of the major descending pathways influencing spinal reflex activity
(adapted from Sheean, 1998b, p.20).
Orange: excitatory pathways. Blue: Inhibitory pathway.

Earlier models of spasticity implicated the muscle spindle, but Sheean (1998) argued that this was based on an inappropriate model (i.e. the decerebrate cat) and highlighted more recent evidence which showed that the muscle spindle in UMN patients is in fact normal (see also Rothwell (1994) and Hagbarth (1994) for a review).

1.2.1.4 Biomechanical contributions to RTPM

Muscle tone as a biomechanical phenomenon

An interesting discussion on the role of biomechanical factors in RTPM can be found in Walsh (1992). Walsh debunked - elegantly and effectively - the commonly held belief that resting tone is the manifestation of minuscule activation of skeletal musculature. Walsh's arguments are based on data from Basmajian (1957), who reported a complete absence of electrical activity in relaxed muscles of normal subjects. In his own work, Walsh (1992) found no change in tone following the administration of anaesthesics and nerve blocking agents in non-impaired subjects. He suggested that stretch reflexes probably did not occur in city dwellers unless they engaged in "combat situations". Similar findings were reported by Thilmann *et al.* (1991), who found no evidence of the stretch reflex in relaxed muscles of non-impaired subjects occurring under speeds of 200 deg/s (which is probably faster than the clinical test for assessing resistance to passive movement). However, in people with spasticity, large, long-duration EMG responses may be found at much lower velocities (Rothwell 1994). Taken together, these findings indicate that "resting tone" in non-impaired subjects has no neural input but represents a biomechanical property of soft tissue instead.

Visco-elastic properties

Elasticity of a material refers to its ability to return to its original form after a deforming load has been removed (Allen et al., 1949) and is defined by its relation between stress (force) and strain (displacement). Viscosity[4], on the other hand, is dependent on the rate of displacement and is therefore expressed in the relation between force and velocity (Walsh 1992). Since soft tissues in the human body display visco-elastic properties, biomechanical methods to measure resistance to passive movement in patients with spasticity are often based on these relationships, with force being measured as a function of (rate of) displacement or vice versa.

[4] According to Walsh (1992), the word "viscous" stems from the Latin "viscus" which means "mistletoe". The berry of the mistletoe contains a sticky liquid, which was used in the past to trap birds.

Hysteresis

Upon loading and unloading visco-elastic material, hysteresis[5] may be observed, which results from the storage and subsequently the release of energy, as the measurement instrument is put through the measurement range. Thus, the output depends on the history of the measurement, i.e. whether this is carried out in an ascending or descending order (Durward et al., 1999).

Typically, the stress-strain curve pertaining to the phase in which the muscle is stretched lies above that pertaining to the phase in which the muscle is returned to its starting position. The area under the first curve represents the amount of energy delivered to the muscle system during the upward phase, whereas the area under the second curve represents the amount of energy absorbed during the return phase (Walsh, 1992). The area within the so-called "hysteresis loop" (i.e. between the first and the second curve) is therefore equal to the net energy loss during one load-unload cycle (Walsh, 1992). Studying the hysteresis loops in patients with spasticity therefore gives an indication of the visco-elastic behaviour of the affected soft tissue.

Thixotropy

Another important non-neurogenic factor that may contribute to RTPM is thixotropy[6], which refers to the phenomenon where changes in a material are caused by motion (Walsh, 1992, p. 84). An example is muscle stiffness, which diminishes with gentle, repeated movement through the range of motion. Hill (1986, cited by Walsh, 1992) attributed this stiffness to the cross-bridges between actine and myosine filaments of muscle tissue. When studying the neural input into thixotropy, Walsh (1992) found that changes in muscle stiffness due to imposed oscillations of the wrist in seven patients with spasticity was in fact accompanied by silent EMG. In addition, thixotropic effects were obtained before as well as after neuromuscular blocking drugs. These findings show that thixotropy is a non-neural phenomenon. Interestingly, thixotropy is temperature dependent. Walsh (1992) cited studies on the effects of cooling on upper limb posture and observed increased flexion of the elbow, wrist and intercarpal joints as a result (Fay and Smith 1941, cited in Walsh,

[5] Hysteresis: from 'υστερησις, i.e. deficiency (Walsh, 1992, p. 195).
[6] Thixotropy: from the Greek θιξις (touch) and τροπη (turning) (Walsh, 1992, p. 84).

1992) – in fact a posture that is common in patients with an UMN lesion. In addition, Walsh (1992) used local cooling of the forearm, which led to increased stiffness and great difficulties for the subjects to perform voluntary movements. These data suggest that thixotropy is relevant for understanding RTPM: stiffness experienced by patients with UMN lesions may partially be attributable to thixotropy caused by immobilisation and it may be further compounded by impaired circulation and thus decreased temperature of the affected limb. Secondly, as the ensuing review will show, some methods for assessing spasticity involve repetitive testing, which could confound the results by reducing thixotropy and thereby the resistance to passive movement.

Contractures, myositis ossificans, loss of sarcomeres and inertia

Other biomechanical factors that may contribute to increased RTPM are soft tissue contractures and in some cases myositis ossificans (Edwards, 2002), which signify a permanent loss of range of movement. In muscle tissue, the loss of range of movement may lead to a reduction in the number of sarcomeres, which may further increase the likelihood and severity of contractures, leading to a vicious circle of immobility and stiffness. Finally, inertia and mass moment of inertia may contribute to RTPM. Inertia is an important factor to consider during spasticity assessment, as inertial affects associated with passive movement (especially when starting, stopping and changing direction of passive movement) may confound the results.

1.2.1.5 Summary

Increased RTPM is a common symptom following an UMN lesion that requires treatment in many patients. Clinicians commonly assess RTPM by means of qualitative scales (e.g. the Ashworth scale). Although these are easy to use, they do not differentiate between the neurogenic and non-neurogenic components of RTPM, one of which could be spasticity, as defined by Lance (1980). However, in order to be able to assess the efficacy of spasticity management, the various factors contributing to RTPM need to be differentiated and measured using valid, accurate and reliable tools. The next part of this section describes a review of the literature pertaining to biomechanical techniques for measuring upper limb spasticity.

1.2.2 BACKGROUND TO THE REVIEW

As explained earlier, there is a lack of agreement in the literature and clinical practice regarding what spasticity is and how to measure it. Against this backdrop, the EU-funded Thematic Network *Support Programme for Assembly of a database for Spasticity Measurement (SPASM)* [http://www.spasmproject.org/] was set up to systematically review the literature on spasticity measurement and put forward recommendations. The SPASM project comprised three strands: the Neurophysiological group (Voerman et al., 2005), the Clinical group (Platz et al. 2005) and the Biomechanical group (Wood et al., 2005), which undertook the task to review methods for investigating non-neural components of spasticity involving the upper and lower limb.

The first challenge facing the SPASM Consortium was to identify a working definition of spasticity. In an attempt to strike a balance between Lance's specific (but narrow) description of spasticity and the broad (but vague) clinical interpretation of the phenomenon, the *SPASM* Consortium proposed the following definition:

> *"Assuming that all involuntary activity involves reflexes, then spasticity is intermittent or sustained involuntary hyperactivity of the skeletal muscle associated with an UMN lesion."*

The following sections present the Upper Limb biomechanical component of the SPASM review. First, the search strategy will be outlined. After presenting a concise overview of the literature, the discussion will revisit the above definition of spasticity and offer some critical comments and suggestions for biomechanical measurement of spasticity of the upper limb.

The search strategy for the SPASM Biomechanical Group in is detailed in Appendix 1.1. The biomechanical review as a whole was led by Wood, who selected relevant papers pertaining to the upper extremity. As indicated in Appendix 1.1, papers were rejected after their full length had been reviewed, if they met the criteria listed in Box 1.1.

Box 1.1

Reasons for the rejection of papers

- Not related to spasticity
- Concerned with measurement and/ or modelling of the non-impaired neuromuscular system - no reference to the UMN syndrome or spasticity
- No inclusion of biomechanical methods to measure spasticity
- Insufficient information on measurement methodology (i.e. abstract only)

A total of 101 relevant papers were identified, of which 45 were rejected. The most common reasons for rejection were that the study was concerned with the non-impaired neuromuscular system and made no reference to the UMN syndrome in general or spasticity in particular (n=28, 63%), followed by papers that did not feature a biomechanical method for evaluating spasticity (n=15, 31%), while only a few papers were rejected as they were abstracts only (n=3, 7%)[7]. Table 1.2 presents an overview of the number of papers originally identified, the number of papers rejected and the final number of papers included in the review.

Table 1.2

Overview of the number of papers for the review of biomechanical methods for measuring upper limb spasticity

Upper limb region	Number identified	Number rejected	Number included
Hand	8	5	**3**
Wrist	14	7	**7**
Elbow	59	21	**38**
Shoulder	2	2	**0**
Upper limb	13	10	**3**
Review papers	5	0	**5**
TOTAL	***101***	***45***	***56***

The overview in Table 1.2 demonstrates clearly that the body of literature pertaining to biomechanical measurement of spasticity involving the hand, wrist, shoulder and upper limb as a whole was very small indeed. In fact, only the body of literature pertaining to the elbow joint was sufficient to enable different categories of methodologies to be compared. Therefore, this review will concentrate on the elbow joint only.

1.2.3 MEASURING SPASTICITY: GENERAL CONSIDERATIONS

In order to be able to categorise and critically evaluate different measurement systems, a number of relevant reviews will be described first.

Price (1990) provided a useful framework for classifying mechanical methods to measure spasticity, although –curiously - he did not define the concept of spasticity itself. Price distinguished the following methods: controlled displacement, controlled torque, gravitational and manual, which are described, together with their strengths and limitations, in Tables 3.3 and 3.4. Price's categorisation of measurement methodologies will form the basis of the review in this chapter. Additionally, the Biomechanical group of the SPASM consortium included the category "functional", which refers to measuring spasticity during active movement. The rationale for this was that the methods, described by Price, evaluated spasticity in passive conditions only. These are not representative of active, voluntary movement (Fellows *et al.;* 1994; Crenna, 1998; Burridge and McLellan, 2000), which are more relevant for clinical purposes. However, in line with Johnson (2002), care was taken not to equate functional outcomes with measures of spasticity, since Johnson pointed out that the relationship between function and Lance's (1980) definition of spasticity is still far from properly understood.

Additionally, Toft *et al.* (1989) provided a valuable overview of which factors need to be standardised during spasticity measurement. The authors emphasised that, in order to be able to interpret the stretch reflex response, the input (i.e. stretch itself) must be standardised. This may be achieved in the following ways: short duration stretches (i.e. less than 15 ms) may be delivered by a tendon hammer with a built-in force transducer. The hammer itself may be manually operated or motor-driven, but the force needs to be standardised. Stretches of a longer duration (i.e. 30 ms or more) may be administered by moving a joint with a motorised device, which enables the velocity and amplitude of the displacement to be standardised. The resulting response from either short or long stretches may then be measured by means of a force transducer and electromyography (EMG). EMG enables both the

[7] One paper did not relate to spasticity *and* did not use a biomechanical method for measuring spasticity and was thus counted double.

short latency response (corresponding to the phasic stretch reflex) and long latency reflexes to be registered – provided the sample frequency is adequate. Toft *et al.* pointed out that the amplitude of these responses depends on background muscle activity, which therefore also needs to be taken into account. In addition, since different aspects of the stretch reflex are elicited under different velocities, the speed of tissue elongation also needs to be considered.

In their thorough overview of the various biomechanical and neurophysiological processes contributing to spastic hypertonia, Katz and Rymer (1989) recommended that spasticity measurement concentrate on the stretch reflex threshold. They suggested that measuring joint stiffness was probably not useful, as this was more likely to indicate contracture rather than reflex hyperexcitability. However, they explained that measuring the stretch reflex threshold on the basis of EMG measures could be problematic, firstly because estimating the point at which the EMG signal appears is not trivial and secondly because different muscles have different thresholds. A mechanical approach, using torque measurements at specified angles, was considered to be more informative. However, the authors cautioned that inter-subject variation in anthropometric variables (e.g. limb mass, muscle bulk) would impact on the interpretation of data unless these differences were accounted for. For intra-subject assessments however, the measurement of torque could be a useful application.

In summary, these reviews highlighted a number of key points that are important to consider when evaluating different spasticity measurement methods:

- For biomechanical spasticity measurement to be valid:
  - simultaneous measures of stretch reflex behaviour or muscle activity are required, since biomechanical measures alone do not distinguish between non-neurogenic and neurogenic contributions to overall resistance to passive movement (RTPM). When measuring stretch reflex behaviour, reflex threshold is probably more relevant than reflex gain.
- For biomechanical spasticity measurement to be reliable:
  - The perturbation needs to be well defined and controlled.
  - Background muscle activity needs to be considered when measuring spasticity

Tables 1.3 and 1.4 indicate the strengths and limitations of the various categories of spasticity measurement methods, which will be further discussed in the ensuing section on methods for measuring spasticity involving the elbow joint.

Table 1.3

Methods for biomechanical measurement of spasticity, as categorised by Price (1990).

HandS: Health and safety

METHOD	BRIEF DESCRIPTION	TYPICAL OUTPUT	STRENGTHS	LIMITATIONS
Manual	The examiner manually rotates a particular joint, usually while the patient is relaxed.	▪ Resistance to passive movement ▪ Joint range of movement	Easy to use in clinical practice	▪ Velocity poorly standardised: ▪ Difficulty maintaining constant velocity within each trial ▪ Difficulty standardising velocity between trials ▪ Difficult to calculate torque
Gravitational	Gravity causes joint motion: the examiner lifts the patient's relaxed limb segment against gravity and then releases it.	▪ number of oscillations ▪ relaxation index ▪ speed ▪ amplitude	Easy to use	Limited scope for upper limb assessment
Controlled displacement Input[8]: ▪ Ramp ▪ Sinusoidal ▪ Random	A motorised method for imposing joint motion whereby the velocity of joint rotation is controlled, using a device where the patient's limb is placed into/ strapped onto.	▪ torque ▪ mechanical work	▪ Standardised input ▪ Velocity dependency of response can be studied	Inertia may confound results More complex (but simpler than for controlled torque) HandS considerations Generally unsuitable for routine clinical use
Controlled torque Input: ▪ Ramp ▪ Sinusoidal ▪ Random	A motorised method whereby the torque applied to the patient's body segment is controlled, using a device where the patient's limb is placed into/ strapped onto.	▪ angular displacement	▪ Standardised input	Limb dissipates proportion of torque during acceleration Complex HandS considerations Generally unsuitable for routine clinical use

[8] Input: different types of input are explained in table 2.4.

Table 1.4

Different types of input for the Controlled Displacement methods described by Price (1990).

ROM: range of movement

INPUT METHOD	DESCRIPTION	STRENGTHS	LIMITATIONS
Ramp	Limb is displaced at a fixed acceleration, then at a predetermined constant velocity, then at a fixed deceleration until it reaches its end position. The phase of interest is the constant velocity phase. Typically, the *threshold* and *gain* of the stretch reflex are measured.	Controlled condition for investigating the velocity-dependent nature of the stretch reflex response	▪ ROM required for acceleration and deceleration phases reduces ROM for the constant velocity phase. ▪ Acceleration itself may alter the reflex response; high accelerations may evoke reflex response due to shock loading ▪ Acceleration and deceleration cause an inertia response, which is superimposed on the actual reflex response.
Sinusoidal	Limb is displaced under fixed amplitude and varying frequency conditions. Typically, the *frequency response* of the stretch reflex is measured.	▪ Well-defined input ▪ Relatively simple equipment ▪ Relatively easy data analysis ▪ Technique enables elastic tissue properties to be distinguished from viscous properties.	Patients may (unintentionally) modulate their response as the input is predictable.
Random	Variable sinusoidal input	The strengths of sinusoidal input without the predictability of the input	Requires more sophisticated equipment than for sinusoidal input.

1.2.4 MEASURING SPASTICITY INVOLVING THE ELBOW

1.2.4.1 Introduction

Fifty-nine papers were identified that described biomechanical methods for measuring spasticity involving the elbow. Only 38 of these could be included, as the other 21 papers did not meet the eligibility criteria; seven did not relate to the UMN in any way, another seven did not measure spasticity, six studies did not use biomechanical measurement methods and one study (which was an abstract only) did not have sufficient information (Table 1.2). Each of the following sections will summarise a specific methodology and highlight those findings that are relevant for the validity and reliability of spasticity measurement. Further details of the studies have been listed in Appendix 1.2.

1.2.4.2 Manual methods

Manual methods have been reported for measuring tonic stretch reflexes (Neilson and McCaughey, 1981), phasic reflexes (Zhang *et al.,* 1997), tonic and phases reflexes (Sherman *et al.,* 2000), RTPM and EMG (Pandyan *et al.,* 2001, 2003b) and tissue compliance (Leonard *et al.,* 2001), while Marchese *et al.* (2001) sought to determine the effects of various biomechanical factors on clinical spasticity assessment. To measure the *tonic stretch reflex (TSR) response* of the elbow flexors, Neilson and McCaughey (1981) described a manual method, using five different amplitudes and two different levels of background contraction. Their subjects (five non-impaired adults, and five adults with CP) were lying in supine on a plinth, their arm strapped into a frame that restricted movement to elbow flexion and extension. The elbow was flexed to 90 deg and subjects were asked to maintain a contraction equivalent to either 10 or 20% of the maximum voluntary isometric contraction of their elbow flexors, stabilising the elbow in its position, while the examiner oscillated the elbow around this position with a constant amplitude and frequency (about 4 Hz), using an oscilloscope for guidance. The five different amplitudes of the perturbations (i.e. peak to peak) were: 1.67, 2.50, 5.00, 7.50 and 10.00 deg. Each of these was maintained for the duration of the trial, which lasted about 1 minute. Elbow angle and EMG data were collected at a sampling rate of

20Hz. Results indicated firstly that the gain of the TSR was greater at the 20% contraction level than at the 10% contraction level. Secondly, within each of the two levels of contraction, the TSR increased with increasing amplitude of the stretch, but not in a linear fashion, so that the actual *gain* of the TSR decreased with increased amplitude. Taken together, these results suggested that the TSR is dependent on the background level of contraction as well as the amplitude of the perturbation. Therefore, Neilson and McCaughey recommended that, when measuring the TSR, that both background contraction level and amplitude of the stretch be controlled.
This method would appear to be relatively easy to perform in the clinic, as it does not involve any motorised parts. Instead – and this is a strength and a weakness - it relies on the consistency of the examiner. However, one might question the accuracy and reproducibility of this method, especially where amplitudes as small as 1.67 deg are involved. In addition, later investigations (Cathers *et al.;* 1996) have shown that subjects may be able to anticipate the perturbations (especially if they are predictable) and thereby contaminate the results, which may have accounted for some of the reflex modulation that was observed in this study. Therefore, a random input paradigm would have been more valid, albeit more complex. An additional point is that the sampling frequency in this study was considerably lower than most studies using EMG in the literature, but this may be attributed to the state of the art at the time. Naturally, a higher rate would be required to register the stretch reflex adequately, which should be attainable with more modern technology.

A method for measuring *tendon reflex gain* (TRG), defined as the ratio of the peak reflexive torque to the peak tendon tapping force (measured in cm), Zhang *et al.,* (1997) used an instrumented tendon hammer. This paper was an abstract only, hence the amount of technical information was limited. The tendon hammer was equipped with a six-axis force sensor, which measured the tendon tap. The reflex response was measured in terms of muscle activity as well as extension torque. For the elbow joint, the triceps brachii reflex was tested. The subjects (n=16: five CVA, five SCI and six non-impaired, age or time after acute event not reported) were seated, with the upper limb stabilised in a position with the shoulder in 90 deg abduction and 15 deg flexion, the arm in a horizontal plane. The device was then locked at a specific elbow flexion angle. It was reported that the tendon tapping was performed with the m. triceps contracting isometrically. The tendon was tapped 20

times, at different levels of force. The results showed that the TRG was higher for the patients than for the non-impaired subjects. Interestingly, it was noted that the TRG of one subject was 30 times higher than the mean value for non-impaired subjects, which would have been difficult to convey on a clinical scale for the tendon reflex. However, although the instrumented tendon tap is a meaningful clinical test, one of its problems is that the vibration, produced during the tap, may also generate a reflex contraction and thereby confound the results. The authors noted that a drawback of this method was the cast, which had to be designed to stabilise the position of the limb to be tested, although suggestions were made to render the method more user-friendly, e.g. by using accelerometers and measuring the tendon bounce-back force.

A range of instrumented versions of standard clinical tests for hyperreflexia, spasticity and paresis was used by Sherman *et al.,* (2000) in their single case study. The following techniques were used: the tendon tap (using a hammer with an in-built load cell to register the force of the tap on the tendon of the m. biceps brachii, together with EMG), response to quick stretch (by means of an electrogoniometer to register elbow movement, together with EMG) and rapid successive movements of the thumb and index finger (using a video-based motion analysis system). Despite showing evidence of hyper-reflexia, there was no evidence of spasticity since there were no qualitative differences in EMG response between the affected and non-affected side, and also because integrated EMG turned out not to be correlated to the velocity of the stretch. In summary, these results indicated a dissociation between hyperreflexia and spasticity, suggesting they are independent phenomena. A weakness of this methodology was its manual nature – and therefore the inevitable variation in input, whilst its strength was the integration between commonly used clinical methods and measurement technology, which facilitates the clinical interpretation of the data.

A manual method for evaluating spasticity involving the elbow was developed by Pandyan *et al.* (2001, 2002b, 2003b, 2004[9]), based on the manoeuvre for the Ashworth scale (Ashworth, 1964; Bohannon and Smith, 1987). The DATA system (Displacement And Torque Analysis), strapped onto the subject's forearm, featured

a strain gauge and a commercially available flexible electrogoniometer. These instruments measured the force applied to the forearm and the resulting elbow angle over time, respectively, as the elbow was moved through flexion and extension.

Resistance to passive movement (RTPM) was defined as the slope of the regression line of each force-angle curve. Additionally, while the Ashworth test was carried out, EMG of elbow flexors and extensors was measured at a frequency of 1000 Hz. Interestingly, the correspondence between RTPM, the Modified Ashworth Score (MAS)[10] and EMG turned out to be poor. In a study with 16 patients one week after stroke, Pandyan *et al.,* (2001) found the association between RTPM and the MAS to be low (κ=0.366). In patients with a MAS of 1+, RTPM was significantly higher than in those with a MAS 1 or 0. However, there was no significant difference in RTPM between MAS scores of 1 and 0. The authors acknowledged a limitation of their study, namely that only the lower MAS scores were represented. A further study with 63 subjects less than 26 weeks after stroke (Pandyan *et al.;* 2003b) yielded similar results: the correlation between RTPM and the MAS was low (ρ=0.511). Furthermore, there was no significant difference in RTPM between MAS scores of "1", "1+" and "2", which questions the hierarchy of the MAS. Pandyan *et al.,* (2001) also set out to quantify the "catch", a feature of scores "1" and "1+" in the MAS. Biomechanically, the "catch" was defined as a transient increase in the force that opposed passive elbow extension. However, in only 11 of the 18 patients with MAS of 1 and three of the six subjects with a MAS of 1^+ was a biomechanical catch registered, indicating a discrepancy between the clinical and biomechanical methods to identify the "catch".

Further discrepancies between changes in RTPM, MAS and elbow flexor EMG were noted in a study investigating the effects of botulinum toxin in chronic stroke patients with upper limb spasticity. In seven of the 14 stroke patients, the MAS remained unchanged whereas EMG decreased. Conversely, in three of the 14 patients the MAS decreased whilst the EMG increased (Pandyan *et al.;* 2002b).

[9] The Pandyan et al. (2001b, 2002b, 2004) publications are listed in Appendix 6.

[10] Scoring criteria for the MAS (Bohannon and Smith, 1987) are: "0": No increase in muscle tone, "1": Slight increase in muscle tone, manifested by a "catch" and release or by minimal resistance at the end of range of motion when the affected part(s) is moved in flexion or extension, "1+": Slight increase in muscle tone, manifested by a "catch", followed by minimal resistance throughout the remainder (less than half) of the range of movement (ROM), "2": More marked increase in muscle tone through most of the ROM, but affected

In summary, these results clearly indicated the lack of correspondence between the MAS and the neurogenic component of spasticity (i.e. EMG) as well as the non-neurogenic component of spasticity (i.e. RTPM), providing further support for earlier concerns about the validity and reliability of the MAS (Pandyan *et al.,* 1999).
The advantage of the DATA system is that it enables the clinician to assess the resistance to passive movement clinically, as well as measure it quantitatively. The device could also be used both in sub-acute and chronic patients. However, the inevitable drawback of a manual system is the difficulty to standardise the rate of displacement. This may be a serious potential confounding variable when measuring the behaviour of a velocity-dependent phenomenon. However, in contrast to the MAS, the device enables the angular speed to be monitored and taken into consideration *post hoc.* In comparison with the controlled displacement and torque methods however, which will be described in subsequent sections, the health and safety as well as practical aspects of this device are considerably more favourable and conducive to clinical applications.

A different manual method for assessing spasticity involving the elbow joint was developed by Marchese *et al.* (2001). Their report details the results from validation studies with 11 non-impaired subjects and 14 stroke patients. The device enabled testing to be carried out in a lying or sitting position, while arm supports could be adjusted to fit the patient. The operator moved the patient's arm by holding a handle and moving this at the rhythm of a metronome. Thus, sinusoidal movements at speeds of 45, 90 and 120 deg/s were generated. Position, torque and EMG signals of the elbow flexors and extensors were sampled at a rate of 25Hz. EMG was used only to assess whether subjects were actively contracting before or during the test but actual EMG data were not reported. Marchese *et al.,* (2001) argued that moment arm of the elbow flexors and extensors, speed of movement and gravity acting on the arm and hand all vary as the elbow angle changes and sought to determine whether these changes were confounding variables. The purpose of their study was also to quantify these changes and develop algorithms that would take these factors into account.

part(s) easily moved, "3": Considerable increase in muscle tone – passive movement difficult, "4": Affected part(s) rigid in flexion or extension".

Although this method was described as easy to use, it involved a large piece of equipment and training was required before clinicians could use it. Being a manual system, velocity was difficult to control but the metronome provided the examiner with some guidance on the frequency of movement. The authors can be commended for their openness regarding the problems encountered with some of their patients; they reported that the equipment was difficult, at times impossible, to use with patients with severe shoulder spasticity. In addition, some problems were reported with the calibration studies and the authors highlighted the need for further work.

A weakness of the methodology was the limited use of EMG data; had this been sampled at an appropriate rate and included in the analysis, the methodology would probably have enabled both neurogenic and non-neurogenic components of spasticity to be addressed.

A different type of manual device, i.e. the Myotonometer, was used by Leonard *et al.* (2001). This is a tissue compliance meter; a probe that pushes onto the muscle and measures the *displacement per unit of force,* i.e. stiffness. Measurements were taken with elbow flexors in a relaxed state and during a maximal voluntary isometric contraction. The sample consisted of ten patients with an UMN lesion (CP or CVA) and ten non-impaired, age-matched controls. A range of isometric forces was used, from 2.5 to 9.8 N., with increments of 2.5N. From these data, length-tension diagrams were generated. Interestingly, in rest, no significant difference was found in tissue compliance between spastic and non-spastic muscles. In contrast, during contraction, increased tissue compliance was found in the affected as well as the non-affected side of the UMN patients when compared with the controls, which indicated decreased tone. According to the authors, this was indicative of paresis of the affected side – although this was not actually assessed.

Although this instrument appeared to be relatively quick and easy to use, the omission of EMG implies that the method would not allow neurogenic and biomechanical causes of stiffness to be differentiated.

1.2.4.3 Controlled displacement methods

Ramp waveforms

Controlled displacement methods with ramp input have been reported more frequently than any other method for investigating biomechanical aspects of spasticity involving the elbow. Typically, this method involves passive elbow flexion and extension at a predetermined velocity profile, while position and/ or velocity, the force or torque of the forearm against the measurement device and EMG of the flexors and extensors are recorded.

As early as 1972, Norton *et al.* used a controlled displacement method to measure spasticity. Ramp-and-hold angular perturbations were used by Dewald and Given (1994) and Dewald *et al.* (1996) in their investigations of the effects of electrical stimulation on spasticity. Repeated testing was used before and after intervention, starting at velocities that would not elicit a stretch reflex. After this, the speed was gradually increased. A noteworthy feature of this methodology was that the starting position and velocity were not standardised but selected on an individual basis in order to obtain a repeatable stretch reflex response from each subject. However, a possible confounding factor in this methodology may have been the repetitive nature of the input, which may result in a reduction of the stretch reflex response (Schmit *et al.;* 2000).

A controlled displacement method was also used by Wolf *et al.* (1996) to investigate whether the starting position of the elbow and the speed at which the muscles were stretched would influence the threshold angle of the stretch reflex. The *threshold angle* was defined as the position of the elbow joint at which the muscle response exceeded baseline EMG by 2.5 SD. Two starting positions (70 and 90 deg flexion) and two speeds (0.5 and 1.0 rad/s) were used. The authors noted that, in some instances, the threshold angle occurred before the intended speed had been reached. The results indicated that the threshold angle was not affected by speed, but that it was affected by the starting position. A starting position of 90 deg flexion and a speed of 1.0 rad/s yielded the most consistent results and this was recommended by the authors in order to standardise testing conditions.

Fellows *et al.* (1993) used a controlled displacement method together with an instrumented tendon hammer in a study with 28 stroke patients and 20 non-impaired controls. The study was designed to compare the response of the m. biceps brachii to imposed elbow extension (representing a tonic reflex) with that to a tendon tap (representing a phasic reflex). The rationale was that, although the tendon tap is a routine test, it does not appear to resemble a stimulus that might be encountered in normal circumstances, in contrast to the imposed displacement. Subjects were placed, according to the time since they had their stroke, in one of three groups: less than one month, one to three months and more than 12 months. For the controlled displacement method, an amplitude of 30 deg/s was used with movement speeds ranging from 80-300 deg/s. For the tendon tap, an instrumented hammer was used, equipped with a switch that initiated EMG recording upon contact with the tendon. Ten repetitions were applied at each speed. Force, position and EMG from elbow flexors and extensors were all recorded. Surprisingly, the tendon jerk response in CVA patients less than one month after stroke did not show any significant increase from that in non-impaired control subjects. Additional discrepancies between the response to the tendon tap and passive movement led the authors to conclude that the tendon reflex may not reflect changes in reflexes evoked under more natural conditions and it therefore provides an incomplete picture of spasticity. These findings were later supported by a single case study by Sherman *et al.* (2000).

Controlled displacement methods were used in a series of studies by a group of investigators, using similar methods (Lai *et al.,* 1996; Ju *et al.,* 2000; Lee *et al.,* 2002), featuring a modified dentist's chair, in which the patient could sit or lie down. The system could be used in a controlled displacement as well as a controlled torque mode. In the study by Lai *et al.* (1996), the apparatus was used in its controlled velocity mode. Four patients with an UMN lesion were involved in a feasibility study. The patient was seated and asked to relax. Their shoulder was positioned in 90 deg abduction, the elbow in 110 deg flexion. The range of motion tested was 45 deg, at one of five speeds: 20, 40, 60, 80 and 100 deg/s. Spasticity was quantified in terms of *stiffness ratio* (measured as the ratio of dynamic stiffness[11]and static stiffness) and *reflex torque* (measured as the difference

[11] Dynamic stiffness is the dynamic torque (DT) registered during the ramp phase of the displacement, but without the reactive torque due to inertial effects. The static torque (ST)

between dynamic torque and static torque). In addition, net EMG was calculated as the difference between elbow flexor and extensor EMG. Finally, correlations between the torque measures and net EMG were computed and the sensitivity of these parameters to the velocity of the stretch was also determined. It was found that both the stiffness ratio and the reflex torque correlated positively and significantly with net EMG activity ($r>0.63$, $p<0.05$), as well as with the velocity of the stretch ($r>0.64$, $p<0.05$). It needs to be noted that the sample was mixed, with 2 CVA, one MS and one PD patient, which may explain the variability in the results. The finding that the biomechanical parameters were velocity-dependent supported Lance's characterisation of spasticity. The authors concluded that the velocity sensitivity of stiffness ratio and reflex torque could be used to quantify spasticity. However, the two weaknesses to be addressed in future work were: high peak torques at the beginning and end of the movement (i.e. artefacts caused by inertial effects of the device itself) and misalignment between the centre of joint rotation and the axis of the device, which may have caused an error in the static torque measures.

Using a similar technique, Ju *et al.* (2000) sought to quantify the development of spasticity following a stroke. They selected two relative torque measures, which avoided the artefacts associated with inertia and which also eliminated stiffness: the *average speed-dependent reflex torque* (or ASRT) and the differentiation of this parameter with respect to velocity – the *velocity sensitivity of the ASRT* (VASRT). Four patients were followed for a period of six months after stroke onset and their affected and non-affected elbows were compared. Patients were lying in supine and asked to relax. Their shoulder was placed in 90 deg abduction and the elbow in 110 deg flexion. No details could be found regarding the positioning of the wrist and fingers, however. The range of joint movement tested was 75 deg at angular velocities of 20, 40, 60 or 80 deg/s, administered in random order. The preliminary data suggested that the ASRT of the affected side was considerably higher than in the non-affected side in most subjects, especially at the higher speeds. The VSART was generally higher in the affected than the non-affected side. In terms of the development of spasticity, the VASRT of both the affected and non-affected side

is the torque encountered during the phase where the elbow position is constant. Stiffness is the ratio of torque and displacement of the elbow. Stiffness ratio = DT/ST.

fluctuated after stroke and tended to decrease in the three to six month period, although there was considerable inter-subject variation.
Although the advantage of this device is that it could provide on-line information about the velocity-dependent component of resistance to passive movement, the authors acknowledged that their device was not practicable in routine clinical practice and that further developmental work was required.

A series of investigations by Schmit *et al.* (1999, 2000, 2001) into the behaviour of the stretch reflex featured a Biodex machine. In their earlier work, two parameters had been identified as indicative of the pathophysiology of spasticity: *angular threshold* and *reflex stiffness*. The angular threshold was defined as the angle at which the passive muscle first shows activation and this was taken as a measure of baseline excitability of the motoneuron. The reflex stiffness, derived from the slope of the torque-angle relationship, was taken as a measure of the reflex loop gain. This portrayed the input- output relationship in terms of the displacement of the joint in relation to the resulting muscle force. Schmit *et al.* (1999) explained that the determination of the angular threshold and reflex stiffness had been based on the assumption that the reflex response is a linear phenomenon. However, they questioned whether this could stem from the fact that previous studies (Powers *et al.;* 1988, 1989) had only used a limited range of amplitudes (i.e. between 30-60 deg/s). In order to investigate whether different amplitudes would have an effect on the stretch reflex, they administered large amplitude (i.e. 90-100 deg), controlled velocity displacement. During testing, subjects were seated with their shoulder positioned in 80 deg abduction and 0 to 10 deg flexion. The wrist and hand were stabilised in a cast, with the hand being fixed to a manipulandum attached to the Biodex motor. In these studies, the speed of extension was selected on an individual basis, in order to produce a stretch reflex at midrange of motion. In addition, a speed of 6 deg/s, below the stretch reflex threshold, was chosen to obtain the passive response of the elongated soft tissues. Data collected comprised torque, position, velocity and EMG from the elbow flexors and extensors. Interestingly, the results indicated that a large proportion of the measurements were non-linear under these large-amplitude conditions; the torque responses tended to reach a plateau, often towards the end of range of motion, which had not been

Reflex torque (RT)= DT-ST.

reported previously. Based on muscle modelling, the authors reasoned that it was most likely that these non-linearities originated from changes in muscle activation patterns, which would not occur during stretches with smaller amplitudes. They concluded that the assumption of a linear torque response to constant velocity ramp stretches may be an oversimplification, based on small amplitude testing conditions, and could lead to errors.

A similar methodology was used in a subsequent study by Schmit *et al.* (2000), which investigated whether the stretch reflex changed with repeated joint movement. Twenty to 30 constant velocity flexion and extension movements (chosen at an individual level, between 30 – 90 deg/s) were administered to the elbow joint, at a frequency of about 1 Hz. Despite considerable variability between subjects in their stretch reflex responses, as well as the ways in which they adapted to the repeated stimuli, the stretch reflex of the elbow flexors decreased in six out of seven subjects. Interestingly, the average reduction in reflex torque of this muscle group was 50% after 30 movements. The authors recommended that these findings be taken into consideration when investigating the effects of treatment on spasticity, as repeated testing may confound the results.

The same equipment was used by Kamper *et al.* (2001) in a study designed to quantify and normalise stretch reflex responses across different muscle groups. Spasticity involving the elbow as well as the finger flexors was measured. Subjects were seated with the shoulder positioned in 80-90 deg abduction and 5 -10 deg flexion. The wrist and hand were stabilised in a cast. Angular velocities were selected in such a way that the resulting elongation of the two groups of muscles would occur at approximately the same rate of change of fibre length, normalised by optimum fibre length. The speeds chosen were: 60, 75, 90 deg/s for the elbow and 200, 250, 300 deg/s for the MCP joints. In addition, a speed of 6 deg/s – at which no reflex was elicited - was chosen to obtain the passive response of the elongated soft tissues. Interestingly, when biomechanical factors, such as fibre length, physiological cross-sectional area and moment arm were taken into consideration, the spastic response of the finger flexors turned out to be greater than that of the elbow flexors. The authors concluded that muscle length is an important factor in determining the magnitude of the stretch reflex response (e.g. reducing the length

reduced the response) and that this should be taken into consideration when measuring spasticity.

Sinusoidal waveforms

A controlled displacement method with sinusoidal input was used by Sahrmann and Norton as early as 1978.

A controlled displacement method with sinusoidal-type input was used by Jobin and Levin (2000) and Levin *et al.* (2000). While the first study involved fourteen children with CP , the second included 12 adult stroke patients and four non-impaired controls. The purpose of both studies was to investigate the regulation of the stretch reflex threshold in muscles around the elbow joint. The *dynamic stretch reflex thresholds* were measured as the angle at which EMG activity appeared at different velocities. The subjects were seated, their shoulder abducted and flexed to 70 deg, while the forearm, wrist and hand were stabilised in supports. Subjects were asked to relax completely during testing. So-called "bell-shaped" velocity inputs were administered in order to simulate the manual procedure for assessing spasticity, commonly used in the clinic. The joint range of movement over which the test was carried out was 100 deg, starting from full flexion. Different mean velocities were used: 8, 16, 32, 53, 80, 120 and 160 deg/s (the highest peak velocity being 360 deg/s). The threshold angle was then plotted against the mean velocity and a straight line was fitted through the data. The intercept of this regression line was used as a measure of the "lambda" control point and the reflex threshold. Levin *et al.* (2000) suggested that the key impairment in motor control following a stroke is the inability to regulate the stretch reflex threshold, which causes impairments in generating specific combinations of net joint torque and joint position. Jobin and Levin (2000) found that the stretch reflex threshold demonstrated good test-retest reliability (ICC 0.73, $p<0.001$), although it did not appear to correlate with their clinical spasticity scale (i.e. a modified version of the Composite Spasticity Index; $r=0.39$, $p>0.05$). This correlation was moderate for the elbow flexors (Spearman's $\rho = -0.75$) and lower for the elbow extensors ($\rho =- 0.69$) (Levin *et al.*, 2000).

1.2.4.4 Controlled torque methods

As indicated in Table 1.4, controlled torque methods for spasticity measurement feature a motorised device whereby the torque applied to the patient's body segment is controlled. Typical dependent variables are angular displacement, sometimes together with EMG of the muscles involved.

A controlled torque method with random input was used by Crago et al (1976) in an interesting study, designed to investigate whether the stretch reflex could be modified through different instructions to the subject (e.g. to resist, co-contract, or not resist). Although only non-impaired subjects were involved, the findings are nevertheless relevant for clinical practice. The subject, who was seated, was required to hold a handle that was attached, via a cable and a pulley, to the shaft of a torque motor. The shoulder was stabilised against a brace, but neither the elbow, which was in flexion and supination, nor the wrist joint were stabilised. Prior to the actual examination of the stretch reflex, the background level of tension of the cable was set at a level that required the subject to resist the tension at 10% of their maximum voluntary contraction level. The motor was then programmed to deliver mechanical disturbances at random times. The stretch reflex response was measured under conditions where the direction of the perturbation was either known or unknown to the subject, as well as conditions where the subject was instructed either to compensate for the displacement or not to intervene. Although actual data were only reported graphically, the authors concluded that the actual stretch reflex response was not notably altered by instructions to the subject. Changes in response to the perturbation did take place, but only after a latency of between 70-320 ms, which increased if the subject did not have information about the direction of the perturbation beforehand.

1.2.4.5 Gravitational methods

A pendulum test for the elbow joint was developed by Lin *et al.* (2001, 2003), using a device with a counter mass of sufficient magnitude to oscillate the arm. A further aim was to develop a biomechanical model for the interpretation of the results. The subject was lying on a plinth in supine with the elbow in 130 deg flexion (full

extension was referenced as 0 deg). The distal part of the forearm and wrist were fixed onto an accessory apparatus by means of an elastic strap. The accessory apparatus also featured a shaft and a weight. The shaft was fixed, through a rotary point, to the midpoint of the plinth. The weight was attached to the end of the shaft to counterbalance the weight of the patient's arm, the mass of which had been calculated on the basis of anthropometric data. Subjects were asked to relax during the testing. Elbow flexor and extensor EMG, as well as angular displacement were measured. The main dependent variables of these studies were *elasticity*, *viscosity*, *threshold angle* and the root mean square (RMS) error resulting from the fit of the data to a mathematical model. The authors explained that, since an accessory apparatus had to be added in order to obtain a pendulum movement, the results from the elbow studies could not be directly compared with those from studies involving the knee, although similar trends, e.g. in the magnitude of passive damping, could be discerned.

From the description, it appeared that trials had to be monitored and that only "qualified" trials were kept. Obviously, transparent criteria for discarding data would need to be developed to ensure reliability. Although this test appears simple to perform, it is limited to the elbow joint. Additionally, health and safety would be a concern in cases where patients presented with elbow contractures; in the original study, people with this characteristic had been purposefully excluded.

1.2.4.6 Functional methods

This category of methods includes studies featuring active movement, normally restricted to elbow flexion and extension and performed in a horizontal plane. Although this category is more closely related to function than any of the previous categories, a more appropriate alternative would probably be "active", since the relevance of the testing conditions for ADL was questionable in most cases.

The study by Fellows *et al.* (1994) was one of the few investigations that explored the role of spasticity and paresis in voluntary arm movements. Subjects were seated in a chair, their forearm positioned in a cast and stabilised with straps. They were asked to perform self-paced, smooth elbow flexion and extension movements at an amplitude of 90 deg, using visual feedback indicating the endpoints of the

movement. The movements were performed at incremental speeds, up to as fast as possible. Different loads were applied to the arm. Interestingly, abnormal antagonist EMG activity was found in the "no-load" condition, whilst in the "load" condition, EMG activity of the antagonist was normal. In the second condition, paresis of the agonist appeared to be the main impairment in performing the movements. The importance of this study lies in the suggestion that the predominantly passive conditions in which spasticity tends to be assessed may not be valid for understanding impairments associated with active movement, which questions the predominant passive-perturbation paradigm of spasticty measurement.

1.2.4.7 Mixed methods

Methods listed under this header feature a combination of measurement methods, listed in Table 1.3.

An example for testing an array of dynamics of the human neuromuscular system is the Programmable Limb Testing System (PLTS), devised by Billian and Zahalak (1983). This device incorporated mixed methods whereby a range of kinematics, kinetics and EMG of the upper limb in different testing conditions could be measured. The apparatus comprised a large testing machine at which the subject was seated, performing a range of static and dynamic tasks at different levels of muscle contraction and at different amplitudes. Although only one non-impaired subject took part in the study, the device could have potential for the investigation of spasticity in some patient groups, pending risk assessment and validation testing.

A combination of a controlled torque method with sinusoidal wave input and random perturbations was used by Ibrahim *et al.* (1993) in a study designed to compare elbow flexor and extensor torque and EMG between active and passive movement. For both conditions, the patient was seated in a chair, both their shoulders positioned in 70 deg abduction and the elbows placed in mid-position between pronation and supination. The forearms were stabilised in a cast. In the active condition, subjects were asked to keep their elbow in 90 deg flexion, by stabilising a voltmeter needle at "zero", whilst a sinusoidal torque (0.3 Hz) was applied to their

forearm. In the passive condition, subjects were asked to relax their arm, placed in 90 deg flexion, while their forearm was subjected to random displacements in the direction of elbow flexion or extension. Stretches of different velocities and amplitudes were applied. Within patients, affected and non-affected arms were compared while comparisons were also made between patients and non-impaired controls. The surprising findings from this study were that in patients, a differential modulation of the reflex response was observed, namely extra activation during passive movement and reduced activation during active movement. These abnormalities were seen in both elbow flexors and extensors but more so in the flexors. Together with the findings by Fellows *et al.* (1994), these findings highlight the limited external validity of the passive perturbation paradigm for testing spasticity with regards to understanding active movement.

In an interesting study, O'Dwyer *et al.* (1996) described an instrument for measuring elbow joint displacement, torque and activity of the m. biceps brachii during active and passive movement. This enabled the investigators to explore the correlation between spasticity, contracture, strength and dexterity in stroke patients. Subjects were seated at a table while their forearm was supported by a horizontal frame. During passive movement, subjects were asked to relax, while the examiner moved their elbow through flexion and extension at peak velocities of 60 and 110 deg/s at two different muscle lengths, i.e. at 90 deg or at 20 deg flexion from full extension. Manual, sinusoidal waveforms with an amplitude of 10 deg were guided by a metronome. The following conditions were used: oscillations around 90 deg flexion at 2 and 3.5 Hz., as well as around 20 deg at 2 Hz. Surprisingly, the results indicated that the majority of subjects with contracture demonstrated no increased tonic stretch reflexes under these conditions and there was no correlation between spasticity and contracture, as is commonly believed. Interestingly, the authors suggested that instead of spasticity causing contractures, the presence of contractures could elicit spasticity. In contrast, there was an association between resistance to passive movement and contracture. From a clinical perspective, the significant correlation between strength and measures of dexterity and the absence of a correlation between spasticity and dexterity or strength were of interest. These interesting data highlight the need for further research into the role of spasticity in active, voluntary movement.

1.2.4.8 Summary

The review in this section showed that the majority of studies on spasticity involving the elbow joint measured joint position, reactive torque and derivatives as well as EMG activity of elbow flexor and extensors. From the raw data, a plethora of outcomes was derived, including absolute measures of reflex threshold and reflex torque, as well as relative measures, e.g. the average speed dependent reflex torque and its velocity sensitivity.

Of all categories of methods listed by Price (1990), the controlled displacement with ramp input method was reported most frequently. However, there is considerable variation in the experimental protocols within this type of methodology, e.g. in terms of positioning of the patient, the amplitude and speed at which the joint was moved and the number of repetitions. Together with the different outcome measures used, these incongruencies make it difficult to pool data and obtain a coherent overview of this area of research.

Many of the devices appeared to be in a prototype stage, with insufficient information on health and safety issues. Most systems appeared to be cumbersome and restricted to the elbow joint, which would not be practicable for a routine clinical setting for a number of different reasons, mostly related to resource issues. Many of the studies using a motorised system required subjects to learn specific tasks and follow complex instructions. This may be feasible for those who are only mildly affected or have made a good recovery, but less so for the more severely affected people – who are more likely to been seen in clinical practice. An alternative method for quantifying spasticity is by instrumenting the more commonly used clinical protocols, e.g. the Ashworth scale, but these systems tended to be manual, presenting specific methodological problems, e.g. the lack of standardisation of velocity.

The following section will discuss the state of the art is biomechanical spasticity measurement methods and will reflect once more on the concept of spasticity.

1.2.5 DISCUSSION

1.2.5.1 Introduction

A total of 56 papers on biomechanical methods for measuring upper limb spasticity met the eligibility criteria for this review. Altogether, this body of literature is considerably smaller than that pertaining to the lower limb (Wood *et al.*, 2005). The majority of the upper limb papers concerned the elbow joint (65%), followed by the wrist (14%) and hand (5%). The shoulder emerged as the least researched topic. Given its complexity, this is not surprising; of all upper limb joints, the shoulder has the highest number of degrees of freedom and thereby poses a considerable engineering challenge. Taken together, these findings suggest that research into biomechanical measurement of spasticity has primarily focused on the elbow joint but has paid relatively little attention to the wrist, hand and the shoulder, where some of the most important clinical problems may be found.

The next section will start by discussing the limitations and sources of error of this review, followed by a synthesis of the state of the art in biomechanical measurement of spasticity. Finally, the concept of spasticity will be revisited before ideas for future research are formulated.

1.2.5.2 Limitations and sources of error

The limitations of this review were firstly that only papers published in English were included; reports in other languages were not reviewed. Future reviews should consider literature in a broader range of languages to give a more representative overview of the state of the art.

This review was restricted to work related to the UMN syndrome or spasticity. Clearly, there is a wealth of literature on the characteristics of the non-impaired movement system, which would have been useful in terms of normative data, but this was considered to be beyond the scope of this thesis. In order to fully understand RTPM in the impaired population however, a sound knowledge of the

relevant biomechanics and neurophysiology of the healthy population across the life span would also be required.
In a similar vein, research pertaining to animals was excluded and although the generalisability of animal research for the human species is always a topic of debate, there is no doubt that some animal research is invaluable for understanding generic motor control phenomena.

One of the exclusion criteria was "insufficient information", but this is subject to judgement of the reviewer. Wherever there was sufficient information in a report to categorise the methodology, papers were usually included but the comment was made that information was limited.

1.2.5.3 Defining and measuring "spasticity"

More than 75% of the studies in this review used biomechanical techniques together with EMG. Since this combined method enables neurogenic components of spasticity to be distinguished from non-neurogenic components, the recommendation for biomechanical studies of spasticity is also to include EMG.

However, despite the tendency for most of the studies to include both biomechanical techniques and EMG, there was considerable variation in the methods employed. Given the relatively small number of publications, the range of techniques and outcome measures (Appendix 1.2) is striking, which made it difficult to compare and contrast findings. There may be a number of explanations for this; firstly, different interpretations of the concept of "spasticity" emerged from the literature. In fact, approximately half the number of papers cited Lance's definition of spasticity (1980), whilst the other half did not define spasticity at all. Even between those authors who interpreted spasticity according to Lance, there was a plethora of outcomes, e.g. threshold speed, latency of the stretch reflex, passive and total stiffness indices (Pisano *et al.;* 2000), net work required to stretch and release muscle groups (Kamper and Rymer, 2000), to mention just a few. Other authors concentrated on phenomena such as muscle tone, hyperreflexia, or range of movement, assuming – implicitly or explicitly - that these phenomena were identical to, or associated with, spasticity. Given these differences in interpretation, it is not surprising that spasticity

has been measured in so many different ways. Clearly, this indicates that there is a need to develop an agreed model that describes and explains "spasticity". This is a necessary step before attempts can be made to standardise the (biomechanical) measurement of this phenomenon.

Equipment: state of the art

Accuracy and reliability

Some of the devices reported in the literature appeared to be in an experimental stage at the time of publication. In general, there was a lack of information regarding the scientific properties of the systems, e.g. accuracy and reliability. Only few authors mentioned any calibration studies, but the majority omitted this important issue altogether. Clearly, this information is required before the data may be interpreted with sufficient confidence.

Health and safety

Information on health and safety issues was equally sparse. Especially when applying measurement methods to patients who may have pain, sensory disturbances and/ or contractures, a thorough risk assessment is required and devices need to be equipped with the necessary safety features. This is a particular concern in cases where motorised devices are used. Some authors mentioned explicitly which safety features they had installed, but in general, this information was rarely reported.

Practical feasibility

With regards to user-friendliness and practical feasibility, many of the methods reviewed featured substantial rigs and specialist testing procedures. In addition, data did not usually appear to be readily available, but required post-hoc analysis. Many studies featured purpose-built equipment, which was not (yet) commercially available. Since all of these factors are likely to hamper the implementation of measurement technology in routine clinical practice, it appears that many of the methods reviewed would require considerable further development to render them suitable for clinical application. All in all, the current review would suggest that the manual techniques have more potential to develop into methods for routine clinical settings than do the controlled methods.

Methodological issues

Sample characteristics

With respect to general methodological issues, the sample size in most studies was small. There was often a lack of information on the suitability of the methodology for patients with different levels of spasticity. Only a few authors mentioned they had encountered difficulties in positioning patients, but these reports were sparse. However, the eligibility criteria and/ or characteristics of the measurement methods would often suggest that primarily patients who had recovered relatively well had been included. For example, the requirement to follow verbal instructions, to move distal upper limb joints in isolation and/ or maintain a certain level of voluntary contraction would probably have been difficult, if not impossible, for patients more severely affected by spasticity, sensory, cognitive and/ or speech and language impairments. Therefore, given the small sample size and apparent selection bias, the external validity of the results from many of the studies reviewed needs to be further explored. This is important for at least two reasons; firstly, patients more severely affected by spasticity are more likely to require treatment and therefore assessment. Secondly, to enhance the content validity of the construct being measured, it is important that methods enable the full range of spasticity to be measured and not just a limited range.

Controlling the input

A criticism of the manual methods for assessing biomechanical aspects of spasticity is that their input is not standardised, which may affect the stretch reflex response. Even in the presence of a metronome or another device whereby speed can be monitored, manual methods would be more variable than motorised devices. However, a practical advantage of these methods is that they tend to be safer than the motorised methods and more practicable in clinical settings.

In order to control either the displacement or the torque applied to the limb, many of the biomechanical studies in this review featured motorised devices. This methodology is based on the (implicit or explicit) assumption that this standardises the input to the system being tested. However, Pandyan (personal communication, 2004) suggested that it is important to be specific about which system is being

tested. For example, in the case where spasticity is interpreted according to Lance, the question is whether standardising velocity or torque at the level of the body segment (i.e. a joint and the muscle groups crossing it) also standardises the input at the level of the stretch reflex, i.e. the muscle spindle. In the case of multipennate muscles, however, where the orientation of muscle fibres and their spindles varies, this is questionable. Instead, the effects of displacement or the application of a certain force to a whole muscle is likely to be dependent on the orientation of the muscle spindle with respect to the direction of the perturbation. Overall however, even if the input were not precisely the same for each muscle spindle, a motorised device would reduce the considerable variation in input, resulting from manual testing procedures.

A problem associated with ramp-and-hold devices is that artefacts may occur due to inertia of the limb (Kamper and Rymer, 2000). In order to reduce these, some authors have chosen for sinusoidal input (e.g. Levin et al; 2000). However, this methods is not automatically free from problems either, as will be explained below.

Variation was also observed with respect to the level of background muscle activity prior to the perturbation. Some investigators required patients to produce a stable level of activity (either 10% or 20% of MVC (Neilson and McCaughey, 1981), 10% of MVC (Crago *et al.,* 1976), whereas others required the muscles to be completely relaxed (e.g. Norton *et al.,* 1972; Ju, 2000; Pandyan *et al.,* 2002b). Many of the investigators requiring complete relaxation used EMG to check that this had indeed occurred. Differences in background activity before testing the stretch reflex have been shown affect the response (Neilson and McCaughey, 1981; Toft *et al.*, 1989) and therefore the results from different studies may not be directly comparable. Again, this is a methodological aspect that requires to be standardised in future.

Predictability of the perturbation

Studies differed with respect to the predictability of the input used in their perturbations; some used random input whereas others used repeated testing of a particular condition. Cathers *et al.* (1996) raised the important question whether the ability of a patient to track the perturbation would influence the output. In order to determine the bandwidth characteristics of signals that could potentially be tracked,

they used a device whereby voluntary tracking performance could be assessed in non-impaired adults. Their subjects managed to successfully track sinusoidal perturbations with frequencies as high as 7 Hz. , which led the authors to caution that reflex activity elicited at frequencies below 7 Hz. may be confounded. However, instructions to subjects (e.g. to relax or resist) did make a difference. Although this study did not include patients with an UMN lesion, it raised an important issue, namely that when assessing resistance to passive movement, patients should be instructed to refrain from tracking the limb. This is less likely with random perturbations, but in cases where they are sinusoidal, they should be unpredictable.

Variation in perturbation

Despite the attempts of many authors to standardise the velocity or torque within their investigation, the literature demonstrated that there was considerable variation between different studies. For the elbow joint, displacement velocities varied from 1.67 degree/s (Neilson and McCaughey, 1981) to 160 deg/s (Lee *et al.,* 2002; Jobin and Levin, 2000; Levin *et al.,* 2000). Clearly, this variation renders it difficult to compare the results and further standardisation will be required.

In his erudite overview of methods for measuring muscle tone and related concepts, Walsh (1992) explained a number of important disadvantages: in contrast to clinical methods, many controlled displacement methods cover only a small range of movement and therefore only yield limited information about the resistance encountered. Methods restricted to low velocities provide limited information on the dynamic response of the muscle group tested and, in actual fact, the output may be dominated by velocity-dependent biomechanical factors (e.g. thixotropy). Walsh also pointed out that isokinetic methods involve considerable inertial forces at the turning points, which need to be considered. Sinusoidal methods, on the other hand, involve both inertial and viscous components, the combined effect of which changes constantly. In other words, when it comes to interpreting data from controlled displacement methods, it is important to understand which components of resistance to passive movement are being tested and which could cause artefacts.

Interpretation of the data

It is probably reasonable to say that, for most clinicians, much of the biomechanical literature is difficult to interpret because of the technical jargon and, moreover, the lack of apparent clinical relevance of the data. A number of investigators have correlated their findings with clinical measures of spasticity, but since these are flawed, it is not surprising that correlations have often turned out to be unimpressive.

The interpretation of the clinical spasticity data presented in the literature was in many cases also hampered by a lack of normative data from age-matched controls and although this is partly a limitation of this review, future studies will need to be include non-impaired controls.

With regard to understanding the role of spasticity in a more functional context, Fellows *et al.* (1994), raised a thought-provoking question. They highlighted the fact that spasticity tends to be assessed while the patient is passive. This, however, does not resemble normal ADL conditions of active, voluntary, goal-directed movement. Indeed, the common denominator in most biomechanical spasticity measurement studies is the perturbation response paradigm, applied to a passive or – in a minority of cases- isometrically contracting muscles.

The organisation of motor control in this passive scenario, however, is likely to be different from that required for planning and executing a voluntary movement. Whilst in action, the reflex loops involved in spasticity may become subservient to the supraspinal processes involved in planning, executing and monitoring active movement (e.g. given that during passive movement there is no need to plan, the Supplementary Motor Area is less likely to be involved). This notion is supported by a number of studies that have shown a low or inconsistent correlation between clinically diagnosed spasticity and active function (e.g. Brown *et al.,* 1987; Lin and Sabbahi, 1999) or that have highlighted the difference in RTPM between active and passive conditions. In other words, the ecological validity of current measures of spasticity has significant limitations and this needs to be considered if the aim is to understand the role of the spasticity in normal and abnormal motor control. In their extensive review of neurophysiological methods for measuring spasticity, Voerman *et al.* (2005) also recommended that spasticity be measured during functional activity.

So what is spasticity?

Approaching the conclusion of this review, it is time to reflect on its core concept: so what *is* spasticity? This review clearly conveys the notion that a single answer does not exist. In fact, the attempts to define "spasticity" as a single phenomenon appear to have fractionated the focus of research and clinical practice, leading to a kaleidoscope of definitions, operational variables and measurement methods. Symptoms as diverse as hyper-reflexia, hypertonia, rigidity, contracture, associated movement, spasm and clonus have all been interpreted as "spasticity". However, research has also clearly demonstrated that, although some of these phenomena may be correlated to some extent, each has a different clinical, biomechanical and neurophysiological signature.

This diversity has led a number of authors (e.g. Sheean 1998, 2001; Fellows *et al.,* 1994) to suggest that spasticity may not be a single phenomenon. Fellows *et al.* (1994) attributed the heterogeneity in expression of spasticity to differences in lesion site between patients. However, there may be a different interpretation altogether, namely that the literature on spasticity may be based on a category mistake. The question "what is spasticity?" appears to be analogous to the question "what is weather"? In this case, it is clear that the question needs to be refined in order to be able to address a more specific aspect of the constellation of phenomena that together make up "the weather". In a similar vein, "spasticity" could be conceptualised as an umbrella term for the collection of "positive" symptoms of the UMN. Similar to the term "UMN", which merely indicates a ballpark of signs and symptoms, the term "spasticity" gives some indication of symptomatology, but requires further specification for the purpose of clinical practice and research.

Hence, a way forward could be to abolish the interpretation of spasticity as a single entity and instead to identify and measure each individual symptom that belongs to the umbrella term "spasticity". Thus, a new definition of spasticity was proposed by the SPASM Consortium as follows:

> "*Disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles*" (Pandyan *et al.,* 2005: p. 5).

This interpretation of spasticity is illustrated in fig. 1.4. It is envisaged that this may lead to more clearly delineated avenues of research and clinical practice, e.g. with a focus on the "hyper-excitability" of specific reflexes, "contracture" or "associated movement". This model would also help explain why "spasticity" manifests itself in so many different ways, as for each patient, the mix of positive symptoms of the UMN syndrome will be unique and may depend on a range of factors, including side, site and severity of the lesion.

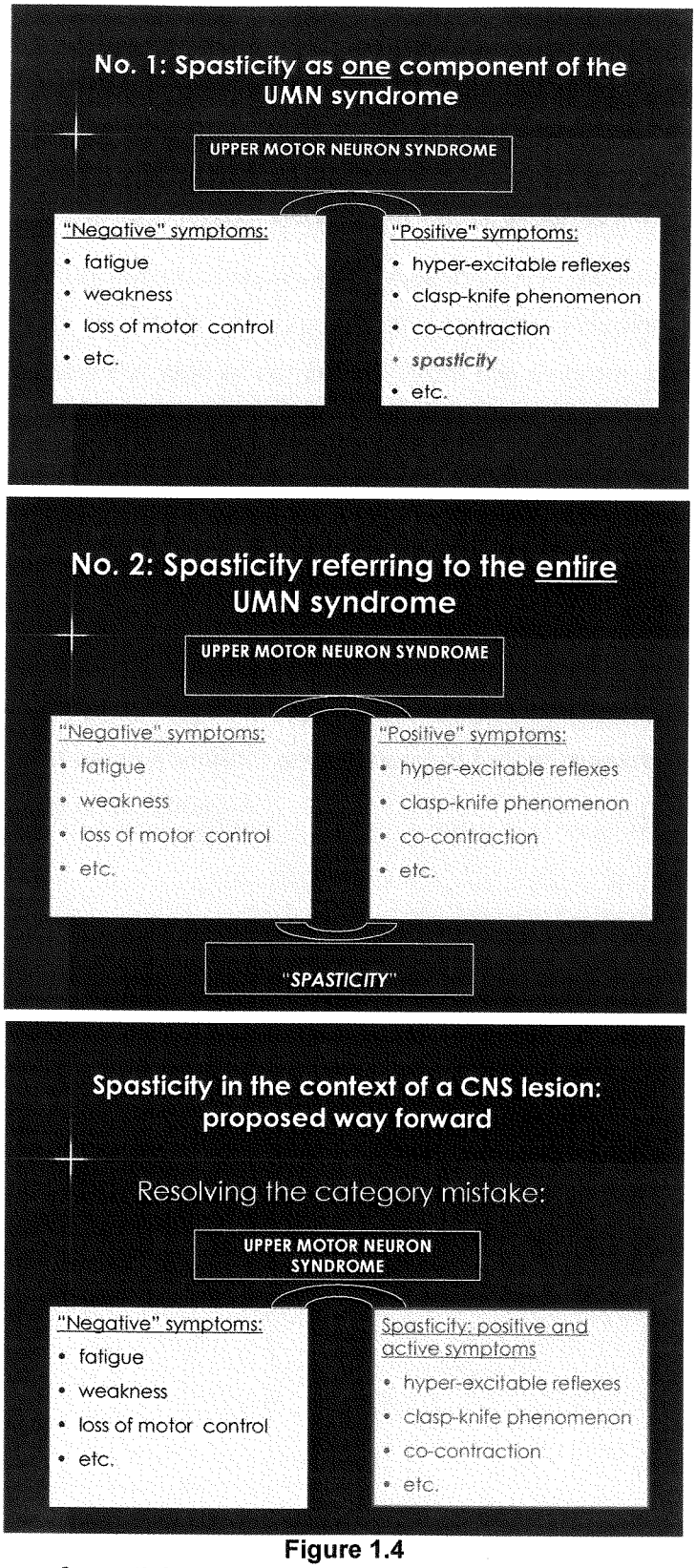


Figure 1.4
Interpretations of spasticity, according to: Lance (top), common clinical practice (middle) and the proposed SPASM definition (bottom)

1.2.5.4 Implications for future research

Figure 2.6 provides a conceptual model that outlines how spasticity research could be progressed. To begin with, "spasticity" will need to be dissected into individual positive features of the UMN syndrome. Based on the WHO International Classification of Functioning, Disability and Health (2001), spasticity research could then be directed at levels of Impairment, Activity Limitation or Participation Restriction (also see Burridge *et al.;* 2005). From this diagram, it is clear that most studies reviewed in this chapter focus on biomechanical aspects of impairment. In contrast, the role of "spasticity" in activity limitations has hardly been explored, while its influence on participation restrictions has not featured in this review at all and highlights an important area for further work.

Another domain, which is not represented the model in fig. 1.5 or indeed anywhere in this review, is that of "negative" symptoms of the UMN lesion, such as paresis. This is recognised as an important area in need of further research (e.g. Gowland *et al.*, 1992; Canning *et al.*, 2004).

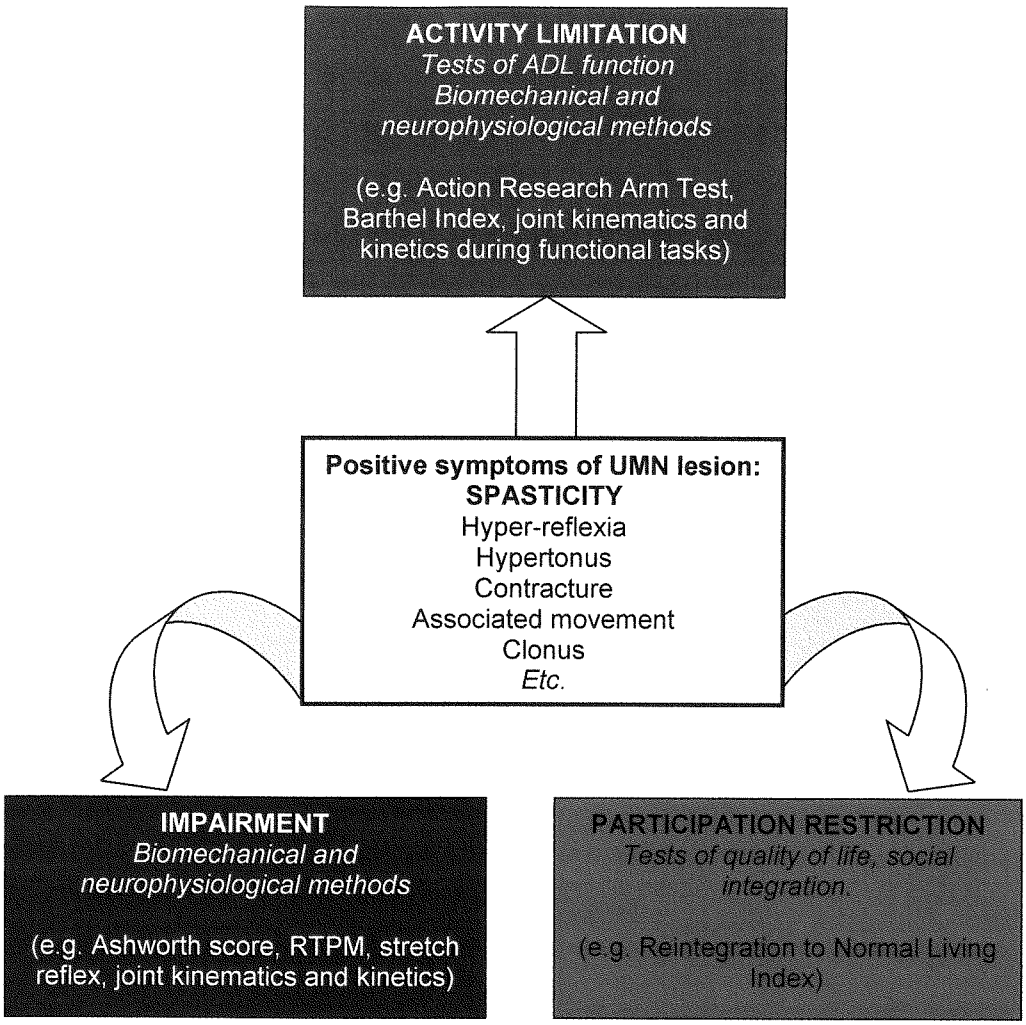


Figure 1.5
Conceptual model for measuring spasticity within the context of the World Health Organisation International Classification of Functioning, Disability and Health.
ADL: Activities of Daily Living, RTPM: Resistance to passive movement, ROM: Range of Movement.

1.2.6 CONCLUSIONS

At present, there is only a limited body of literature concerning the biomechanical measurement of upper limb spasticity, with the majority of publications focusing on the elbow joint. Most of the technology, however, appeared to be in the experimental stage with purpose-built devices. The lack of information on scientific robustness of the measures and particularly on health and safety issues meant that many of these methods would require considerable development before they could be considered for routine clinical practice. Another limitation was that many techniques appeared to be suitable only for patients with mild degrees of spasticity and no significant cognitive or speech and language impairments. However, it could be argued that these patients are perhaps less likely to require intervention (and thus have their spasticity assessed) than those with more severe spasticity.

It is clear from this review that there is a need to develop methods for the biomechanical measurement of upper limb spasticity that:

- Clearly define the construct being measured,
- Have established accuracy and reliability,
- Are suitable for those patients whom are likely to be seen in clinical practice,
- Address the hand, wrist and shoulder joints,
- Include a sufficient set of normative data to enable data to be interpreted
- Where appropriate, address the barriers to implementation in clinical practice.

In order to be able to realise these recommendations, the prerequisite was to clarify the concept of "spasticity". The suggestion put forward was that instead of defining spasticity as a single phenomenon, it be interpreted as an umbrella term for the active, positive symptoms of the UMN syndrome. By identifying precisely which symptom is being targeted, research and clinical practice are able to move forward towards developing more specific avenues of research and clinical practice.

Chapter Two will report pilot work, featuring a novel spasticity measurement device for the elbow joint, which incorporates a number of the recommendations listed above.

Before this, the next section of this literature review will continue on the theme of spasticity by critiquing the evidence underpinning a specialist therapeutic technique for treating focal spasticity, i.e. intramuscular botulinum toxin type-A. In particular, it will focus on the methodologies used for evaluating the effects on spasticity, bearing in mind the recommendations from this review.

1.3 BOTULINUM TOXIN FOR CHRONIC UPPER LIMB SPASTICITY AFTER STROKE

1.3.1 INTRODUCTION

Having discussed the concept of spasticity and critically evaluated different biomechanical methods for measuring this phenomenon, this section will continue by systematically reviewing the evidence underpinning the treatment of spasticity, using botulinum toxin type-A.

As indicated in section 1.1.2, a considerable proportion of people require treatment to reduce spasticity after stroke, for which a range of options is available. Pharmacological methods may be either systemic (e.g. oral Baclofen, Tizanidine or Dantrolene sodium) or local (e.g. intrathecal Baclofen, phenol or botulinum toxin) (Ward and Ko Ko, 2001). Systemic, oral anti-spastic medication may have unwanted side effects that outweigh the therapeutic benefits; e.g. drowsiness or muscle weakness (Ward and Ko Ko, 2001). In cases where spasticity is expressed as a local problem, focal pharmacological agents such as botulinum toxin[1] (BTX) are usually preferred. The latter is used increasingly, as its effects have been shown to be local and involve few side effects, while its administration is relatively straightforward (Barnes, 1997; Hesse, 2000; Davis and Barnes, 2001). There are seven different serotypes of BTX (Types A-G), of which type-A (BTX-A) is used most commonly in clinical practice, while research into the effects of the other types is ongoing.

The administration, effects and side effects of BTX-A in stroke have been described in detail by Davis and Barnes (2001). Briefly, BTX-A acts by inhibiting the release of presynaptic acetylcholine and this decrease in cholinergic transmission at the neuromuscular junction leads to a reduction in tone (Simpson, 1980). Following this chemical denervation, axonal sprouting and gradual reinnervation take place, resulting in full recovery of the neuromuscular junctions, usually after a period of 2-6 months (Davis and Barnes, 2001).

[1] Botulinum toxin (BTX-A) is produced by the bacterium *Clostridium botulinum*.

In order to critically appraise the evidence underpinning the efficacy of BTX-A on upper limb spasticity in stroke patients, a systematic review of the literature was carried out, which will be presented in the next section. The review focussed on the effects of BTX-A on spasticity and resistance to passive movement, grip force, global function in general and upper limb function in particular, as well as care and carer burden in terms of ADL. In order to form a more comprehensive picture of any treatment-related effects, outcomes rated by the treating therapist (or physician), as well as the patient were included.

The quantity and quality of the publications will be described first, after which the strengths and limitations of the evidence base will be discussed.

1.3.2 METHOD

1.3.2.1 Inclusion Criteria

In order to obtain as comprehensive a picture as possible of the quality of research on BTX-A in stroke, prospective as well as retrospective studies, experimental, quasi-experimental and pre-experimental designs (categorized according to Cook and Campbell, 1979, cited in Wagenaar, 1990) were all included[2].. Following initial screening, publications were excluded if they belonged to one or more of the following categories: 1) reviews and overviews – although these were included in the final discussion of the literature, 2) comments or letters to the editor, 3) abstracts or meeting reports, 4) duplicate publication, 5) studies with heterogeneous participant populations, from which the effects on stroke patients could not be discerned, 6) studies with non-impaired participants, 7) studies including treatment of upper limb (UL) and lower limb (LL), from which the effects on the UL could not be isolated, 8) studies with participants younger than 18 years of age, 9) types of BTX other than BTX-A, or 10) language of publication other than English, French,

[2] Electronic databases searched for studies published up until October 2004 were: Medline (via FirstSearch, from start of database), CINAHL (from start of database), Psych_Info 1887 (from 1887), the Cochrane Library (from start of database) and Science Citation Index Expanded (via Web of Science, from 1981), with no restrictions regarding the type of article or language of publication. Search terms used were: (CVA OR cerebrovascular accident OR stroke) AND Botulinum toxin AND Spasticity AND (upper limb OR arm OR hand OR wrist OR finger*).

German, or Dutch. A diagnosis of stroke by means of clinical examination only was accepted. References from the articles obtained through the initial search were further traced by hand.

1.3.2.2 Evaluation Criteria

The literature was evaluated according to the Physiotherapy Evidence Database (PEDro) scale (Appendix 1.3), accessed from:
[http://www.pedro.fhs.usyd.edu.au/korean/scale_item_korean.html#criterion_2]
Using a dichotomous scale, scores range from 0-10, with higher scores indicating better quality. In contrast to the PEDro guidelines for criterion 4[3] however, only in cases where there were differences at baseline and these had been taken into account, using appropriate statistical techniques (e.g. ANCOVA), was this criterion scored with a "yes".

1.3.3 RESULTS

1.3.3.1 Quantity of the evidence base

The initial search yielded 215 papers. Following screening and further tracking of secondary references by hand, a total of 23 papers met the eligibility criteria and were included in this review. Only 7 of these were true-experimental (i.e. double-blind RCTs); one was quasi-experimental (i.e. a between-group study without randomization) and 15 were pre-experimental (i.e. observational cohort or case studies).

1.3.3.2 State of the art: efficacy of BTX-A in stroke patients with upper limb spasticity

Details of the studies reviewed are listed in Appendix 1.4. The effects of BTX-A were categorised according to the three dimensions of the International Classification of Functioning, Disability and Health [http://www3.who.int/], i.e. Impairment, Activity Limitation and Participation Restriction. In the following section,

[3] Criterion 4 on the PEDro scale states that: "the groups were similar at baseline regarding the most important prognostic indicators – no/yes".

results from RCTs will be discussed in detail, whilst those from remaining studies will be described only briefly.

Impairments

Resistance to passive movement (RTPM)

Resistance to passive movement was the most commonly reported outcome measure; it featured in all 7 RCTs and 13 of the 16 remaining studies. In all bar one (Das and Park; 1989a, b, appearing to be a duplicate publication), was RTPM operationalised as either the Ashworth (AS) or modified Ashworth scale (M)AS. Only in one observational study (Miscio *et al.*, 2004) was RTPM of the wrist additionally quantified in terms of passive and total joint stiffness, assessed by means of a controlled displacement device.

Unequivocally, the results from the RCTs indicated that BTX-A significantly reduced RTPM of the muscles injected (Simpson *et al.*, 1996; Hesse *et al.*, 1998; Bakheit *et al.*, 2000, 2001; Bhakta, 2000; Brashear *et al.*, 2002; Childers *et al.*, 2004). Typically, an improvement of 1 point on the (M)AS was observed between one and six weeks after injection, with RTPM returning to baseline at about three months. In addition, there was evidence to suggest that this effect was dose-dependent (Simpson *et al.*, 1996; Childers *et al.*, 2004; Hesse *et al.*, 1992). Further evidence (Childers *et al.*, 2004) showed that a second injection continued to be effective, at which point the effects were no longer dose-dependent. Similar results were found by Lagalla *et al.* (2000) in an observational study following 9 patients over 3 years, in which BTX-A was administered every 3-5 months over a two-year period. In fact, Lagalla *et al.* (2000) found that the period between repeat injections became significantly longer over time. Overall, the results from the remaining studies (Das and Park 1989; Bhakta *et al.*, 1996; Girlanda *et al.*, 1997; Konstanzer *et al.*, 1993; Lagalla *et al.*, 2000; Miscio *et al.*, 2004; Page *et al.*, 2003; Panizza *et al.*, 2000; Rodriquez *et al.*, 2000; Rousseaux *et al.*, 2002; Sampaio *et al.*, 1997; Wang *et al.*, 2002; Woldag and Hummelsheim, 2003) were congruent with those from the RCTs.

Stretch reflex characteristics

Interestingly, none of the RCTs included any measure of stretch reflex behaviour, which three of the observational studies did address. The study by Miscio *et al,* (2004) was the only one that included both non-neurogenic and neurogenic aspects

of RTPM. This study included measures of the stretch reflex threshold speed and the stretch reflex area, evoked during controlled wrist displacement at 500 deg/s. The stretch reflex threshold speed is a measure of the excitability of the stretch reflex, while the stretch reflex area represents the magnitude of the stretch reflex response. This methodology was based on work by Pisano *et al.* (1996, 2000), described in section 1.2. The results indicated that BTX-A injected into the forearm flexors increased the stretch reflex threshold speed and reduced the stretch reflex area for a period of approximately 60 days after treatment, indicative of an overall damping of the stretch reflex response. However, data were only provided in diagrammatic format, which hampered a comprehensive understanding of the results.

Miscio et al. (2004), Panizza et al. (2000) and Girlanda et al. (1997) also measured the Hoffmann reflex and the M-wave from the median nerve. Girlanda *et al.* (1997) found H_{max} to be reduced, while Miscio *et al.* (2004) reported that both H_{max} and M_{max} decreased "dramatically", although supporting evidence was scant. None of the 3 studies found any effect on the H_{max}/M_{max} ratio. The finding that BTX-A reduced H_{max} was interpreted as evidence that its effects were peripheral, while the lack of effect on the H_{max}/M_{max} ratio was taken as additional support for the hypothesis that BTX-A does not affect the excitability of motor neurons.

Force

Muscle force was measured in two of the seven RCTs and eight of the 16 remaining studies. The most commonly used tool was the Medical Research Council scale, whilst a hand-held dynamometer tended to be used for the evaluation of grip force.

In contrast to the expectation of paresis following injection with BTX-A, the force produced by the muscles injected did not necessarily deteriorate. Bhakta *et al.* (2000) found no effect of BTX-A on isometric force of shoulder abductors, elbow flexors and extensors, nor on wrist flexors and extensors. Grip force was reduced, although it was not clear whether this was due to the intervention or between-group differences at baseline. Simpson *et al.* (1996) reported no impact of BTX-A on grip force in the high and medium dosage groups (i.e. 300U and 150U Dysport respectively), but surprisingly, the low dosage group (75 MU BTX-A (Dysport)) actually improved on this parameter at six and 16 week follow-up, even though the forearm flexors had not actually been injected. The authors tentatively suggested

that BTX-A might "unmask" function in adjacent muscle groups, although this was not further explained.

From the pre-experimental studies, the effects of BTX-A on muscle force were mixed. For example, Rodriquez *et al.* (2000) found grip force to be decreased at 3.5 days following injection, in contrast to Wang *et al.* (2002), who noted a significant improvements in both grip- and pinch force over a 12-week period. Woldag and Hummelsheim (2003) noted a varied pattern in terms of impact of BTX-A on grip force and concluded that injecting BTX-A into finger flexors did not necessarily affect grip force. Interestingly, they also observed that the release rate improved in seven out of 10 participants, but the statistical significance of this finding was not reported.

Activity limitations

Functional benefits of BTX-A were assessed in terms of global function and independence, care and carer burden, as well as focal arm function.

Global function and independence

Global function was included in four of the seven RCTs and five of the 16 remaining studies, with the most commonly used tools being the Barthel Index (BI), Functional Independence Measure (FIM), Rivermead Motor Assessment (RMA) and the SF-36. Results from the RCTs clearly demonstrated that BTX-A had no effect on global functioning or independence (Bakheit *et al.,* 2000, 2001; Simpson *et al.,* 1996). The only exception was Childers *et al.* (2004), who found an improvement on the SF-36 in their low dose (90U Allergan) at week six only, which they explained as a placebo effect. Simpson *et al.* (1996) attributed the lack of impact of BTX-A on overall function by the fact that their participants, who were on average three years post stroke, already achieved high scores on the FIM at baseline. This could indicate that the patients in their study had adapted to their condition and that the FIM had reached its ceiling. In addition, Bakheit *et al.* (2000, 2001) argued that these global scales suffer from limited sensitivity and, furthermore, that they include functions that are not expected to change with focal spasticity treatment (e.g. continence) anyway. Conversely, these global tools may fail to include specific aspects of function or care that may be prime targets for treatment, e.g. cleaning the palm of the hand (Childers *et al.,* 2004). Therefore, Bakheit *et al.* (2000) suggested that

individualised goal attainment scales could be more valid and sensitive instruments for the specific purpose of evaluating effects of BTX-A on UL function.

Results from the remaining studies were congruent with those from RCTs; BTX-A had no or minimal effect on global function (Girlanda *et al.,* 1997; Hesse *et al.,* 1992; Rousseaux *et al.,* 2002; Wang *et al.,* 2002). Das and Park (1989) noted improvements between 0-15% on the Barthel Index, but whether these were clinically significant is debatable.

Care and carer burden

Changes in specific care ADLs were evaluated in five RCTs (Bhakta *et al.,* 2000; Bakheit *et al.,* 2000, 2001; Brashear *et al.,* 2002a; Hesse *et al.,* 1998). There was only limited evidence that the tools used had been validated and therefore the results were debatable, but since clinically relevant concepts were addressed and the studies had been adequately controlled, their findings will be described below.

In a trial evaluating the effects of BTX-A combined with electrical stimulation of the UL muscles, Hesse *et al.* (1998) evaluated tasks commonly affected in stroke patients with UL spasticity, i.e. putting the affected arm through a sleeve, opening the hand in order to clean the palm and cutting finger nails. Appendix 1.4 details the design of this study, which included four groups. The group receiving BTX-A plus electrical stimulation improved significantly more in terms of cleaning the palm of the hand than did the groups receiving BTX-A or the placebo injection, although the difference between the first group and those receiving a placebo injection with electrical stimulation was not significant. Bakheit *et al.* (2000, 2001) included the same items as Hesse *et al.* (1998). In both studies, positive changes were found four weeks after BTX-A, on all tasks for all groups (including considerable improvements on two of the tasks for the placebo groups), but a statistical analysis was not performed on these data in either study. Bhakta *et al.* (2002) incorporated similar items in their composite disability scale (rated by the patient) and carer burden scale (rated by the carer), and found a significant reduction at two and six weeks following treatment, with the effects wearing off towards week 12. Simpson *et al.* (1996) also used a caregiver dependency scale, but did not include any details. They found no significant change on this outcome measure in any of the groups, which they attributed to the finding that their participants also scored high on the FIM, indicating that they had adapted to their condition. Brashear *et al.* (2002a)

used the Disability Assessment Scale (Brashear *et al.*, 2002[b]), which included four areas: hygiene, dressing, limb position and pain, from which one area was selected as the principal treatment target. The results indicated that a significantly greater proportion of participants in the experimental group achieved their principal target at week six, compared to the control group, but there were no details as to the nature of these targets. None of the observational studies specifically addressed care or carer burden, although some of the patient-centred goal attainment scales (e.g. Bhakta *et al.*,1996, see previous section) may have included elements of care.

Upper limb function

Upper limb-specific outcomes were evaluated by means of standardised outcome tools (i.e. the Action Research Arm Test (ARAT), Rivermead Motor Assessment/ Upper limb section (RMA/UL), Frenchay Arm Test (FAT), as well non-standardised tools such as purpose-developed scales and questionnaires. Some studies evaluated functional UL activities, e.g. being able to put the affected arm through a sleeve, opening the affected hand in order to clean the palm or cutting finger nails (e.g. Bakheit et al,. 2000), but it was not always clear to what extent these involved activity generated by the patient or their carer.

Surprisingly, despite their focus on the upper limb, none of the seven RCTs utilised a dedicated outcome measure to evaluate UL function. Only two RCTs featured a validated, published outcome measure that comprised functional UL movements, but neither study found any significant improvements in upper limb function (Simpson et al., 1996, Bhakta et al., 2000).

Thirteen of the 16 remaining studies explicitly addressed arm function. Only six of these used standard UL tests; the others featured tools for which no evidence of standardisation/ validation was provided. Hesse *et al.* (1992) used the upper limb section of the RMA, but did not find any improvements. However, since their study involved participants with no arm function, this finding could be attributed to a floor effect. The upper limb section of the RMA was also used by Woldag and Hummelsheim (2003), who found a significant improvement at week 12 following injection. This was interesting, since finger flexor spasticity had already started increase at week four following injection. From the raw data, it appeared that the overall improvement was relatively small for all bar one participant. Rousseaux *et al.* (2002) analysed their data with an ANOVA - despite the fact that the RMA/UL

only yields ordinal level data. Interestingly however, their analysis suggested that the significant improvement on RMA/UL could be attributed entirely to a single item, i.e. picking and placing a tennis ball. Concurrently, Rousseaux *et al.* (2002) found significant improvements in selected grasp activities in ADL, evaluated on an apparently non-validated tool. This, in turn, was possibly facilitated by an improvement in active opening of the first commissure. On the Nine Hole Peg Test, however, no changes were found, which was attributed to the fact that only few patients could carry out this task in the first place. The Frenchay Arm Test (FAT) was used by Sampaio *et al.* (1997), who reported a significant improvement during the course of their study, but no post-hoc analysis was carried out to determine at which time this emerged. The most frequently occurring improvement in their study was 1 point, with the maximum being 3 points in one patient. Interestingly, the authors remarked that most of their patients did not consider the gain in function to be meaningful. The FAT was also used by Lagalla *et al.* (2000), but they reported no statistics other than an improvement in 8/28 of the participants and no change in the remaining 20. Finally, in a single case study where BTX-A was injected following a period of constraint-induced treatment, Page *et al.* (2003), noted further improvements on the ARAT and Fugl-Meyer.

In summary, a considerable number of observational studies used outcome measures for which there was no evidence of standardisation or validation. Given this limitation, together with the fact that the studies were not adequately controlled, the results will not be described here. Further details pertaining to the outcome measures used can be found in Appendix 1.4.

Patient self- assessment

A measure of overall treatment effect, rated by the physician, patient, carer or all three, was included in four of the seven RCTs. Commonly, this included an ordinal level scale, on which the amount and direction of change following BTX-A treatment was indicated (e.g. from "much improvement" to "much worse"). There was no indication in the literature that these tools had been validated, but because of the importance of the patient's perspective, the results will be described below. Overall, participants in the experimental groups tended to derive significantly more benefit from treatment than did the placebo groups (Bakheit *et al.,* 2001, Brashear *et al.,*

2002, Childers *et al.,* 2004, Simpson *et al.,* 1996). Interestingly, Bakheit *et al.* (2001) found that 92% of participants in their experimental group indicated they had obtained much or some improvement following BTX-A, compared to 50% in the placebo group, with the results from the physicians' ratings being similar. Brashear *et al.* (2002) reported comparable results, e.g. throughout the course of their 12-week study, 67-81% of participants in the experimental group indicated they improved at least one point on their scale, compared with 29-48% of those in the placebo group – again with results being mirrored in the physicans' ratings. Not all participants receiving BTX-A improved though; Simpson *et al.* (1996) found significant improvements on both the patients' and physician's global rating scale in their low and high dosage groups (i.e. 75U and 300U of BTX-A (Dysport)), but not in the 150U group. In contrast, Childers *et al.* (2004) observed a significant improvement in the middle and high dose groups (i.e. 180 and 360 MU of BTX-A (Allergan), respectively) compared to the control groups, but not in the low-dosage group (although data were not provided). However, they acknowledged that their dosage was lower than comparable studies, which may have accounted for the absence of effects.

1.3.3.3 Quality of the evidence base

The overview of the methodological strength of the studies in table 3.1, expressed in PEDro scores, indicates that the overall quality of the studies in this review was low (median 2, range 1-10).

A strength of the literature was that most studies (87%) had adequate follow-up, with only three suffering from more than 15% drop-out. In terms of information provided, the majority of studies (65.2%) presented measures of central tendency and variation – however, whether these measures were appropriate to the nature of the data is open to debate, as the PEDro system does not consider this.

Of the 23 studies, only seven were RCTs (30.4%), their PEDro score ranging from 7 to 10. All RCTs were randomised, but in only three studies was randomisation concealed. This is an important weakness, as this could have introduced experimenter bias when allocating participants to their group. In terms of blinding, all RCTs were double-blind, but Bakheit *et al.* (2000, 2001) gave no indication that the clinician injecting BTX-A had also been blinded, which could have introduced

bias. In all other studies, placebo and BTX-A vials had been prepared by personnel not otherwise involved in the trial and/or had been made to look identical. In five RCTs, the experimental and control groups were comparable at baseline. In Bhakta *et al.* (2000) and Hesse *et al.* (1998) however, there were differences between the two groups in terms of age, levels of impairment and disability at baseline, which could have confounded the results. Finally, only four of the RCTs clearly indicated they carried out an "intention to treat" analysis. With respect to the quasi-and pre-experimental studies, this item had been given a positive score if there was clear indication regarding the precise treatment (i.e. dosage, site) had actually been administered.

Table 1.5 Methodological quality of studies evaluating the efficacy of botulinum toxin (BTX-A) in stroke patients according to PEDro criteria (n=23). Allocation: R: Random, C: concealed. Baseline comp.: baseline comparability, Between-gr comp.: between group comparison, P: Participant, T: Therapist, A: Assessor, Point est. and var.: point estimate and measure of variability. Y (N): criterion has (not) been met.

Author (year)	Allocation		Baseline comp.	Between-gr comp.	Blinding			Adequate Follow up	Intention to treat	Point est. and var.	TOTAL SCORE
	R	C			P	T	A				
Bakheit *et al.* (2000)	Y	N	Y	Y	Y	N	Y	Y	Y	Y	8
Bakheit *et al.* (2001)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Bakheit *et al.* (2002)	N	N	N	N	N	N	N	Y	N	Y	3
Bhakta *et al.* (1996)	N	N	N	N	N	N	N	Y	N	Y	3
Bhakta *et al.* (2000)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9
Brashear *et al.* (2002)	Y	N	Y	Y	Y	Y	Y	N	Y	Y	8
Childers *et al.* (2004)	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	9
Das and Park (1989)	N	N	N	N	N	N	N	Y	N	N	1
Girlanda *et al.* (1997)	N	N	N	N	N	N	N[4]	Y	N	Y	2
Hesse *et al.* (1992)	N	N	N	Y	N	N	N	Y	Y	N	3
Hesse *et al.* (1998)	Y	N	N	Y	Y[5]	Y	Y	Y	N	Y	7
Konstanzer *et al.*,(1993)	N	N	N	N	N	N	N	Y	Y	N	2
Lagalla *et al.* (2000)	N	N	N	N	N	N	Y	N	N	Y	2
Miscio *et al.* (2004)	N	N	N	N	N	N	N	Y	Y	N	2
Page *et al.* (2003)	N	N	N	N	N	N	N	Y	Y	N	2
Panizza *et al.* (2000)	N	N	N	N	N	N	N	N	Y	Y	2
Rodriquez *et al.*,(2000)	N	N	N	N	N	N	N	Y	N	N	1
Rousseaux *et al.* (2002)	N	N	N	N	N	N	N	Y	Y	Y	3
Sampaio *et al.*,(1997)	N	N	N	N	Y	N	N	Y	N	N	2
Simpson *et al.* (1996)	Y	N	Y	Y	Y	Y	Y	Y	N	Y	8
Wang (2002)	N	N	N	N	N	N	N	Y	Y	Y	3
Woldag *et al.* (2003)	N	N	N	N	N	N	N	Y	Y	Y	3
Yelnik *et al.* (2003)	N	N	N	N	N	N	N	Y	Y	N	2
Included (n)	**7**	**3**	**5**	**8**	**8**	**6**	**8**	**20**	**13**	**15**	
Included (%)	**30.4**	**13.0**	**21.7**	**34.8**	**34.8**	**26.1**	**34.8**	**87.0**	**56.5**	**65.2**	

[4] Assessor was blinded for a selection of the outcome measures, but it is unclear whether assessors for the other outcomes were also blinded.
[5] Patients appeared to have been blinded for BTX-A, but not for the additional intervention, i.e. electrical stimulation.

1.3.4 DISCUSSION

1.3.4.1 Research quantity

A total of 23 studies, published between the start of the various electronic databases and October 2004, met the eligibility criteria for this review. Only seven of these were RCTs, the remaining 16 were quasi-experimental (N=1) or pre-experimental cohort or case studies (n=15). Compared with the 272 studies identified by Bhogal *et al.* (2003) in their systematic review of the quality of stroke rehabilitation research – which did not include pre-experimental designs – this appears to be a relatively small body of evidence.

1.3.4.2 Research quality

The median PEDro score of the literature reviewed indicated that most studies were of low quality. However, looking at the scores in Table 3.1, their distribution appears to be bimodal, with the RCTs scoring favourably, whilst the remaining studies – the majority– scored poorly. However, some of the observational studies reported innovative treatment (e.g. Yelnik *et al.,* 2003) or measurement methods (e.g. Miscio *et al.,* 2004), which would have slipped through the net of a more selective review.
Although the PEDro system was useful for obtaining first impression of the quality of published work, it failed to address more specific methodological issues, which will be included in the discussion below.

Study design

As indicated earlier, about two thirds of studies in this review were inadequately controlled, which may have biased their findings. The considerable placebo effects, reported by Brashear *et al.* (2002) and Childers *et al.* (2004), highlight the importance of RCTs in this domain of rehabilitation. However, RCTs are not necessarily free from bias; e.g. Simpson *et al.* (1996) used increasing dosages in their RCT. Although their design may have introduced bias, it made sense in terms of safety, which had not been established at the time.
One of the limitations of the PEDro system is that it includes a criterion for between-group design and randomisation, but not for the rigour with which the placebo is

controlled. For example, Hesse *et al.* (1998) used a combination of BTX-A and electrical stimulation and although the BTX-A condition was properly placebo-controlled, this did not appear to be the case for the electrical stimulation condition. In conclusion, more proper, placebo-controlled RCTs are required to strengthen the evidence in this area of research.

Sample characteristics

Size

In the RCTs, mean sample size, not counting for attrition, was 66 (SD 36) ranging from 24 (Hesse *et al.,* 1998: 4 groups) to 126 (Brashear *et al.,* 2002: 2 groups). Only Bakheit *et al.* (2001) and Childers *et al.* (2004) included a power analysis to justify their sample size – although these were based on ordinal level data. Thus, a number of studies (notably Hesse *et al.*, 1998 and Simpson *et al.*, 1996) may have had insufficient power to protect against a Type II error (Bland, 2000). This is a common problem in neurological rehabilitation (Kwakkel *et al.,* 1999a; Pollock *et al.,* 2003) and can often only be resolved through multi-centre trials.

Representativeness

Six of the seven RCTs excluded participants with fixed contractures (Bakheit *et al.,* 2000, 2001; Brashear *et al.,* 2002; Childers *et al.,* 2004; Hesse *et al.,* 1998; Simpson *et al.,* 1996) and so did nine of the pre-experimental studies. However, the method for establishing this exclusion criterion was not described in any of the publications. Therefore, there is a possibility that some patients with joint stiffness due to a combination of non-neurogenic and neurogenic factors – which is very common in chronic stroke patients (Edwards, 2002) – were excluded and this would have affected the external validity of the results.

Potential confounding variables

Botulinum toxin administration

Appendix 1.4 illustrates an almost perplexing variation in BTX-A administration in terms of dosage, sites and methodology (i.e. with or without EMG guidance). Some studies used a standard protocol (e.g. Bakheit *et al.,* 2000, 2001; Bhakta *et al.,* 2000), whereas others favoured an individual approach, according to the clinical symptoms presented (e.g. Lagalla *et al.,* 2000; Miscio *et al.,* 2004; Panizza *et al.,*

2000). Without going into any further detail, it is clear that different sites and dosages could account for some of the differences in results.

Time after stroke

There was considerable variation in terms of the amount of time since the acute event; some participants were included as early as two weeks after stroke (Bakheit *et al.,* 2002), others as late as 42.5 years (Bhakta *et al.,* 1996) after their stroke. Since natural recovery could contribute to improvements at least in the first three months following the acute event (Wade *et al.,* 1983; Nakayama *et al.*, 1994), and learned non-use and biomechanical tissue changes could hamper improvements in the later stages, the amount of time post stroke could constitute a confounding variable. Therefore, future studies should include a more homogeneous sample in terms of time after the acute event.

Levels of impairments/ activity limitation

Most of the RCTs stipulated specific eligibility criteria in terms of resistance to passive movement, e.g. MAS $\geq$ 2 in finger flexors, wrist and elbow (Bakheit *et al.,* 2000), but these varied across studies. Only 13 of the remaining studies reported such criteria and thus their population may have been more mixed in this regard.

In many studies, the precise level of UL function at the start of the intervention was not entirely clear. Only Bhakta *et al.* (1996, 2000) and Hesse *et al.* (1992, 1998) specifically included only patients with no arm function, whilst Wang *et al.* (2002) excluded patients who had no grip force or limited UL movement. Girlanda *et al.* (1997) stipulated that residual arm function must be present, although it was unclear what this involved. Rodriquez *et al.* (2000) required a trace of finger extension with a flexed wrist and Woldag and Hummelsheim (2003) only included patients who were able to activate finger flexors and extensors.

Taken together, this variation in level of impairment and activity limitation makes it very difficult to determine the effects of BTX-A. In future, larger studies where patients are stratified according to their level of arm function and spasticity would be helpful in order to predict more accurately which clusters of patients might be expected to obtain which effects from BTX-A intervention. Rousseaux *et al.* (2002) suggested that an improvement in arm function was best explained by control of thumb and index at baseline, whist improvement in dressing using the affected UL

was best explained by initial level of RTPM of the elbow flexors and level of active wrist extension. Although these data emerged from a pre-experimental study, they are clearly worth further investigation.

Previous/ Concurrent treatment

All RCTs excluded participants with previous focal antispastic treatment, in order to avoid any carry-over effects from previous interventions. However, the presence of concurrent intervention (i.e. physiotherapy and/ or occupational therapy) varied considerably. In 18 of the 23 studies, additional physiotherapy and/or occupational therapy had been provided. Hence, in these cases, the effects of the entire treatment "package" - and not just BTX-A – had been evaluated, although this did not appear to have been acknowledged explicitly. Details pertaining to the content and intensity of additional therapy were patchy; in the RCTs, they were either not reported (Bakheit *et al.,* 2001) or only partially reported (Bakheit *et al.,* 2000), whilst others stated that therapy remained "unchanged"- but without giving any details (Bhakta *et al.,* 2000; Brashear *et al.,* 2002[6]; Childers *et al.,* 2004; Simpson *et al.,* 1996).

Only Hesse *et al.* (1998) provided information on the frequency and content of accompanying physiotherapy. In fact, this was the only study that set out to compare the effects of different combinations of BTX-A with another form of treatment, i.e. electrical stimulation of the injected muscles. Interestingly, they found that electrical stimulation improved some of the outcomes, which highlights the fact that additional therapy may confound the results.

The level of detail in the remaining studies was mixed. An exception was the study by Rodriquez *et al.* (2000), which gave an extensive description of their rehabilitation programme (Appendix 1.4).

Given the variation between studies in terms of therapeutic input and/ or antispastic medication accompanying BTX-A, it is clear that many of the investigations may have suffered from confounding variables. It is imperative therefore, that future studies provide more detailed descriptions of concurrent therapies and control for their possible effects, so that the effects of BTX-A *per se* may be identified.

[6] Note that this only became apparent in the ensuing Editorial, New England Journal of Medicine 348 (3), Jan. 2003, pp 258-259.

Similarity at baseline

Although treatment groups in RCTs were often reported to be "similar", this was not always confirmed statistically (Bakheit *et al.,* 2000, 2001). For example, in the study by Bhakta *et al.* (2000), the experimental group appeared to be less affected in terms of disability and grip force at baseline, whereas mean age in the control group was lower than in the experimental group, which could all have confounded the results. It is a weakness of the PEDro system that it does not require differences between groups to be formally checked at baseline, which a proper interpretation of the data would clearly require.

Follow-up

Follow-up periods varied, but most investigators tended to follow patients over a course of three to four months. In contrast, not all studies reported their findings over this period, e.g. Bakheit *et al.* (2000, 2001) re-assessed patients at weeks four, eight, 12, and 16, but reported most of the outcomes only at week four. In contrast, Childers *et al.* (2004) re-assessed their patients at week one, two, three, four, five, six, nine, 12, 18 and 24 and were able to provide interesting diagrams, illustrating the change within different treatment effects. However, the drawback of multiple comparisons is the increasing the family-wise error rate, which needs to be controlled (Field, 2000). This, however, may render studies vulnerable to a Type II error.

Data presentation and analysis

Although the PEDro system includes a criterion for the presence of point estimates and measures of variability, it is limited in that it does not include an evaluation of the actual appropriateness of these measures. Numerous studies expressed ordinal level data in terms of means and standard deviations without any justification (e.g. Brashear *et al.,* 2002; Childers *et al.,* 2004; Hesse *et al.,* 1998; Panizza *et al.,* 2000; Rousseaux *et al.,* 2002; Simpson *et al.,* 1996). Data presentation was poor in some of the studies, e.g. raw data were presented only in diagrammatic form (Miscio *et al.,* 2004; Rodriquez *et al.,* 2000) or omitted p-values (e.g. Miscio *et al.,* 2004; Rodriquez *et al.,* 2000). A further weakness of the PEDro system is that the appropriateness of the statistical analysis is not included as a criterion. The use of

parametric statistics was frequently used without reassuring the reader that the prerequisites had been met (e.g. Bakheit *et al.,* 2000, 2001; Panizza *et al.,* 2000; Rousseaux *et al.,* 2002; Woldag and Hummelsheim 2003). Quite a few authors included repeated measures, but did not acknowledge the problems associated with multiple comparisons (e.g. Girlanda *et al.,* 1997; Miscio *et al.,* 2004; Wang *et al.,* 2002).

Outcome assessment

Assessing spasticity

In terms of outcomes, Appendix 1.4 displays the vast array of tools that were employed, some of which showed evidence of extensive creativity on behalf of the authors. On the one hand, this may be attributed to the complexity of the syndrome being evaluated, which spans the three pillars of the ICF. On the other hand however, this may be associated with difficulties in operationalising the key concept of spasticity to begin with. In fact, only four authors actually defined "spasticity" – all referring to Lance's 1980 definition. A plethora of related terms was used, including hypertonia, muscle tone dysfunction and spastic hypertonia. Van Kuijk *et al.* (2002) noted a similar observation, namely that none of the studies included in their systematic review clearly differentiated between spasticity and other forms of hypertonia. In terms of measuring spasticity, it was striking to note that 19 of the 23 studies used the (modified) Ashworth Scale, including all RCTs. One study only (Miscio *et al.,* 2004) attempted to quantify spasticity and differentiate between neurogenic and non-neurogenic components of resistance to passive movement.

A further concern was the finding that investigators applied the (M)AS to limb segments for which the scales have not been properly validated, e.g. the fingers (Bakheit *et al.,* 2000, 2001; Bhakta *et al.,* 1996; Brashear *et al.,* 2002; Childers *et al.,* 2004; Hesse *et al.,* 1992, 1998; Rousseaux *et al.,* 2002; Sampaio *et al.,* 1997; Woldag and Hummelsheim 2003) and the thumb (Hesse *et al.,* 1992). Childers *et al.* (2004) reported a 9-point Ashworth scale, with a resolution of 0.5 points but with no evidence of validation[7].

[7] This method was criticised by Pandyan *et al.* (2005, Appendix 6).

Section 1.2 already discussed various problems associated with the measurement of spasticity and highlighted those pertaining to the (Modified) Ashworth Scales in particular. These will not be re-iterated here, but it is important to emphasise that the evidence from RCTs regarding the effects of BTX-A on upper limb *spasticity* in adult stroke patients is based entirely on an outcome measure that is seriously flawed.

Thus, it is evident that problems with spasticity measurement impede evidence-based practice in neurological rehabilitation and that better measurement systems are required to improve this situation.

Types of tools

This review indicated that the majority of outcomes used were ordinal level scales, including global disability scales (e.g. the Barthel Index, Functional Independence Measure) and focal arm function scales (e.g. the Action Research Arm Test, Nine Hole Peg Test). Clinical goniometers were used in a small number of cases, but some authors translated range of movement data into ordinal level scales, thereby reducing the sensitivity of the measure. Actual measurement technology was scarcely used and included hand-held dynamometers to measure grip force (e.g. Rodriquez *et al.,* 2000), video to record movement (Rodriquez *et al.,* 2000), a 3D motion analysis system (Woldag and Hummelsheim, 2003), a controlled displacement torque motor to measure RTPM (Miscio *et al.,* 2004) and physiological instruments to measure the stretch reflex (Girlanda *et al.,* 1997; Miscio *et al.,* 2004, Panizza *et al.,* 2000). These data confirm the impression from the survey into the use of measurement technology, which reported the limited use of measurement instrumentation in neurological rehabilitation (van Wijck *et al.,* 2001, App. 6)

Scope

The consensus emerging from the literature was that the global disability scales were generally not useful; they lacked sensitivity and specificity and often appeared to suffer from floor- or ceiling effects and instead, a number of authors (e.g. Bhakta *et al.,* 1996; Hesse *et al.,* 1998; Bakheit *et al.,* 2000, 2001; Brashear *et al.,* 2002[a]) recommended the use of more specific scales instead. This literature review suggests that outcomes that focus on a select number of self-care ADLs (commonly cutting one's finger nails, washing hands and sliding the paretic arm through a

sleeve) are indeed more sensitive. A strength of these test items is that they tend to be more patient-centred, which is congruent with the current shift in clinical practice towards more involvement of the service user (Chartered Society of Physiotherapy, 2002). However, an important weakness of these items is that there was little evidence to indicate they had been validated. The first paper in which the personal self-care activities, mentioned above, were described was the study by Hesse *et al.* (1992), but they seemed to serve as mere examples. The same items were then used by Bakheit *et al.* (2000, 2001) without reference any other research. Although there is some indication that these items are indeed clinically relevant for some patients, further validation is required.

In a similar vein, a number of authors used outcome measures including a global assessment of treatment effects and disability scales, without providing any evidence that these had been validated (e.g. Childers *et al.,* 2004; Girlanda *et al.,* 1997; Konstanzer *et al.,* 1993; Panizza *et al.,* 2000; Wang *et al.,* 2002), which constitutes a clear weakness in the evidence base. Again, before the results arising from these scales can be properly understood, validation is required.

Outcome measures and the ICF

Most of the outcome measures in the body of literature reviewed here reflected impairments, with some addressing specific activity limitations. However, there is an apparent dearth of information on the effects of BTX-A on participation restrictions. This could be explained by the fact that the databases searched include primarily biomedical research. Alternatively, it may reflect the predominantly biomedical paradigm from which health care professionals tend to approach the management of spasticity. It is obvious that future work is needed to explore the effects of BTX-A treatment on participation. This is necessary to yield a more comprehensive understanding of the effects of spasticity treatment on the lives of people who have had a stroke.

In conclusion, this literature review clearly indicates that the evidence for the efficacy of BTX-A in the treatment of adult stroke patients with spasticity is not only largely restricted to the assessment of impairments, but also that most of it – especially pertaining to the primary outcome, i.e. spasticity – is conceptually flawed. The first

priority for new investigations should be to select valid and, where possible, quantitative measures of spasticity, validate specific clinical outcome measures (e.g. those including specific care ADLs) that are thought to be particularly useful and incorporate all three pillars of the ICF in the assessment battery.

1.3.4.3 Evidence for the effects of BTX-A

Having discussed the amount and robustness of the evidence underpinning the use of BTX-A in the treatment of UL spasticity after stroke, the next section will present the main conclusions regarding the impact of BTX-A on RTPM and spasticity, muscle force and different aspects of function.

RTPM and spasticity

In order to determine the effects of BTX-A, results from the RCTs was used primarily. Overall, there was clear evidence to indicate that BTX-A reduced RTPM in the limb segments being treated (Bakheit *et al.,* 2000, 2001; Bhakta *et al.,* 2000; Brashear *et al.,* 2002; Childers *et al.,* 2004; Hesse *et al.,* 1998; Simpson *et al.,* 1996). However, these reductions were not always statistically significant for all limb segments at all points of assessment. The magnitude of this effect was usually a decrease of 1 point on the (modified) Ashworth scale, observed between one and six weeks after injection, returning to baseline around 12 weeks afterwards. These findings echoed those from earlier reviews (van Kuijk *et al.,* 2002, Fève *et al.,* 1998, Hesse 2000, Muller and Wissel 2001, Richardson and Thompson, 1999, Rousseaux *et al.,* 2003).

In contrast, this review revealed a dearth of evidence regarding the effects of BTX-A on the stretch reflex, the key concept in spasticity according to Lance, or its resultant output (i.e. muscle activity). It is clear that further work is required in this domain.

Muscle force

Although it would be plausible to expect a decrease in force following BTX-A, there was little evidence to this effect. Interestingly, some reports indicated that grip force actually increased following BTX-A and this could be explained in cases where BTX-A reduced RTPM of the finger flexors, which then offered less resistance to active wrist extension, which in turn improved the length-tension relationship of the finger

flexors and enhanced grip force. Alternatively, in patients with preserved UL function, an increase in force may have been an indication that the affected limb was used more in ADL. In any case, the effect of BTX-A on force is not clear at present and would require further research.

Global function, care and carer burden

The evidence from four RCTs indicated that BTX-A had no impact on global function, but this was attributed to a lack of sensitivity, specificity, floor and ceiling effects of these scales, as well as to the fact that some of the more chronic patients may actually have adapted to their condition (Simpson *et al.,* 1996, Bakheit *et al.,* 2000, 2001, Childers *et al.,* 2004). Instead, investigators in five RCTs introduced scales for selective care-related ADLs (Bhakta *et al.,* 2000; Bakheit *et al.,* 2000, 2001; Brashear *et al.,* 2002; Hesse *et al.,* 1998). The results were mixed, data were generally poorly reported and statistical analysis could often not be performed. Additionally, there was no evidence in most of these studies that the outcome measures had been validated.

In terms of global improvement, as rated by the physician and/ or the patient and/ or carer, significant improvements were found along the course of treatment (Bakheit *et al.,* 2001; Brashear *et al.,* 2002; Childers *et al.,* 2004; Simpson *et al.* 1996). However, two RCTs (Bakheit *et al.,* 2001; Brashear *et al.,* 2002) also revealed considerable placebo effects and it needs to be noted that there was no evidence that the outcome measures had been validated.

Arm function

A common assumption is that by reducing RTPM, BTX-A improves PROM, which facilitates AROM, which in turn promotes function (Muller and Wissel, 2001; Rousseaux *et al.,* 2003; Teasell *et al.,* 2003, Francis *et al.*, 2004). However, the evidence from the stroke literature yielded only two RCTs that evaluated arm function with a standardised tool and both showed no significant difference (Simpson *et al.,* 1996; Bakheit *et al.,* 2000). Performing a meta-analysis on the two RCTs by Bakheit *et al.* (2000, 2001), Francis et al. (2004) attempted to show functional improvements in arm function following BTX-A, but this was undermined by their use of unvalidated outcome measures, which comprised a mix of selected items from existing clinical scales. Additionally, the term "function" appeared to

have been interpreted somewhat widely, with outcomes reflecting care items, which might or might not require any activity on behalf of the patient.

Other explanations for the dearth of evidence for the impact of BTX-A on arm function could be methodological (i.e. limitations of the outcome measures), but may also be related to sample characteristics, e.g. severe paresis, learned non-use, or contractures.

Taken together, is clear that there is a dearth of evidence regarding the benefits of BTX-A in terms of actual function. Since functional gain is probably of more relevance to patients and clinicians than a mere reduction in RTPM (Thompson, 1998), further research in this area is needed urgently.

1.3.5 CONCLUSIONS

The body of literature on the effects of BTX-A on stroke patients with UL spasticity, reviewed up until October 2004, was relatively small (i.e. seven RCTs, one quasi- and 15 pre-experimental studies). The overall methodological quality of the RCTs was generally good, according to the PEDro criteria, whilst that of the remaining studies was poor.

So what is the impact of BTX-A in stroke patients with UL spasticity? The results from this review indicated that this question is not easy to answer. In their systematic review, van Kuijk *et al.* (2002) suggested there may be two clusters of patients, each obtaining differential effects from BTX-A. In severely affected patients, BTX-A may facilitate positioning and care of the affected limb. However, more robust tools need to be developed to ascertain the efficacy of BTX-A in the area of (self) care and future studies could stratify participants according to baseline levels of function and spasticity in order to tease out the differential effects of BTX-A in these two proposed clusters of patients. Patients with mild spasticity and some remaining activity in their UL extensors may obtain some specific functional benefit from BTX-A – although this review showed that the evidence on this point is very limited.

The results clearly indicated that BTX-A was effective in reducing RTPM, but this evidence was based almost entirely on the Ashworth scales (Ashworth 1964, Bohannon and Smith 1987), which have been criticised (Pandyan *et al.,* 1999). The review found a dearth of quantitative evidence distinguishing between the effects of

BTX-A on the non-neurogenic and neurogenic components of RTPM; none of the RCTs used a measure of reflex behaviour or muscle activity to represent actual spasticity. BTX-A did not necessarily reduce muscle force, but further work is required to elucidate this effect. Effects of BTX-A on global function and care could not be demonstrated, but only a very small number of RCTs addressed these parameters and the outcome measures were generally of poor quality. Furthermore, issues related to participation had hardly been addressed in this body of literature – despite reports on their importance after stroke (Barnes and Ward, 2000; Dekker *et al.*, 1995; Lai *et al.*, 2002).
Surprisingly, the effects of BTX-A on actual functional activity involving the affected arm had hardly been explored, which highlighted the need for further research.

One prominent issue in this review was the finding that many of the studies did not describe the specifics of concurrent treatment - which was commonly provided - in sufficient detail. In these cases, it was therefore unclear which effects were due to BTX-A and which were associated with the additional therapeutic input.
In order to elucidate this issue, the next section of this chapter will further explore the literature on BTX-A and report evidence on the differential effects of treatments, when provided together with BTX-A.

1.4 BOTULINUM TOXIN AS PART OF A COMPREHENSIVE TREATMENT PROGRAMME

1.4.1 INTRODUCTION

The observation in the previous section, namely that the majority of studies featuring BTX-A provided concurrent treatment, is not surprising, given that the guidelines for BTX-A treatment in adults with spasticity recommend that:

> *"Botulinum toxin injection must be part of a rehabilitation programme involving post-injection exercise, muscle stretch and/or splinting to achieve an optimal beneficial clinical effect"* (Barnes *et al.*, 2001: p.3[1]).

This recommendation is based on the view that, by reducing excessive α-motoneuron activity, BTX-A offers a window of opportunity for achieving other treatment goals (e.g. Bhakta, *et al.*, 1996; Sheean, 1997; Hesse, 2000, 2001; Bhakta, 2000; Richardson and Thompson, 1999; Graham *et al.*, 2000), which may be further facilitated through additional forms of treatment.

The question addressed in this next section of the literature review is: what is the evidence to support this guideline recommendation? Which combination of interventions, including BTX-A, is most efficacious for a particular goal? Specifically, in cases where the goal is to improve UL function, what is the most effective rehabilitation programme? In order to answer this question, the evidence from studies investigating the differential effects of additional interventions, when combined with BTX-A will be discussed next.

1.4.2 BTX-A IN UPPER LIMB REHABILITATION IN STROKE

Section 1.3 presented a systematic review of the literature on the effects of BTX-A on the upper limb following stroke. In fact, the differential effect of additional treatment, provided with BTX-A, had been investigated in only one of the 23 studies: Hesse *et al.* (1998) investigated the effects of additional electrical stimulation (ES) in a group of stroke patients with so-called "non-functional" arms. The study included four treatment groups: BTX-A injection plus ES, BTX-A only, placebo injection plus

[1] This guideline can also be found in the Guidelines for the use of botulinum toxin (BTX) in the management of spasticity in adults, issued by the Clinical Effectiveness and Evaluation Unit of the Royal College of Physicians (2002: p. 5).

ES and placebo injection only. ES was applied to the flexors and extensors of either the wrist or elbow. Over the course of a 12-week period, the results were in favour of the group treated with BTX-A plus ES (e.g. greater reduction in Ashworth score, greater perceived ease of cleaning the palm of the hand). The additional benefits of ES were explained by referring to animal experiments, which had shown that ES accelerated the rate of BTX-A uptake. Although Hesse's (1998) study had a number of limitations (i.e. small sample size, with six subjects in each group, no placebo control for the ES condition), it was innovative in that it was the first in this field to systematically compare BTX-A with additional treatment.

No other studies were identified from the review in section 1.3 that evaluated the differential effects of additional treatments, when administered together with BTX-A.

1.4.3 BTX-A AND NEUROLOGICAL REHABILITATION IN GENERAL

In order to broaden the field, a further literature search was conducted, including upper and lower limb, as well as a wider range of central nervous system disorders. The following electronic databases were searched for studies published up to and including November 2004: Medline (via FirstSearch, from start of database), CINAHL (from start of database), Psych_Info 1887 (from 1887), the Cochrane Library (from start of database) and Science Citation Index Expanded (via Web of Science, from 1981), with no restrictions regarding the type of article, nor the language of publication[2]. Only a further two studies were identified from this search, but since they concentrated on the lower limb, they will only be summarised below.

Hesse *et al.* (1995) compared the effects of two different BTX-A interventions in patients with hemiparesis and lower limb spasticity due to a stroke. One group (n=5) was injected with BTX-A into their ankle plantar flexors, while the other group (n=5) received additional, alternating ES of the m. tibialis anterior and plantar flexors for 30 minutes per session, six times per day for three weeks following the

[2] Search terms used were: (CVA OR cerebrovascular accident OR stroke OR MS OR Multiple Sclerosis OR HI or head injury OR TBI OR traumatic brain injury) AND Botulinum toxin AND Spasticity AND (therapy OR treatment OR intervention OR physiotherapy OR physical therapy OR occupational therapy OR splint* OR cast* OR tap* OR electrical stimulation OR exercise OR motor learning OR skill acquisition OR stretch*).

injections. The results suggested that the group with the ES improved more than the other group in terms of a reduction of resistance to passive movement (RTPM) and a number of gait parameters. As in their 1998 study described above, the results were explained through the enhanced uptake of BTX-A, mediated by ES. Although this study had several limitations, notably in terms of internal validity (i.e. ES was not placebo-controlled, the design was quasi-experimental and the sample size was small), it is noteworthy for its original question. A number of other studies have emerged since, in which BTX-A was combined with ES (e.g. Rodriquez *et al.,* 2000; Johnson *et al.,* 2004), although none of these established the differential effects of the added intervention.

Finally, in a single-blind RCT with 18 chronic stroke patients with equinovarus feet associated with severe spasticity, Reiter *et al.* (1998) compared an intervention consisting of 190-320 MU BTX-A (Allergan) injected into up to five lower limb muscles with an intervention using a single injection only of 100 MU BTX-A (Allergan) into the m. tibialis posterior, combined with ankle strapping. Patients were followed over a period of 90 days. In terms of resting position, passive range of movement and resistance to passive movement, the group with the multiple injections derived more benefit than the other group. Interestingly however, with respect to gait (measured as time taken and number of steps needed to walk 10 m. independently), both groups improved significantly and to a similar extent, while patients in the combined treatment group also reported that walking felt easier and that they walked more frequently (which may actually have been a confounding variable). This study is interesting from a health-economics perspective, as it showed that a lower dose of BTX-A may be as effective as a higher dose in terms of improving activity, when combined with additional (and probably lower-cost) treatment.

No other studies could be identified, which compared the effects of BTX-A alone with a combined treatment programme including BTX-A. Additionally, no studies were found where the effects of a particular treatment programme were compared with the same programme supplemented with BTX-A.

1.4.4 CONCLUSIONS

BTX-A may be administered for a number of different reasons, ranging from facilitating more passive functions such as hygiene and positioning, to improving active ADLs. The question addressed in this section was, which combination of treatment strategies (including BTX-A) would be most efficacious for a particular treatment goal, especially improving UL function after stroke.

This section showed that, in the general neurological rehabilitation literature, there was very little published evidence to demonstrate the differential effects of other treatments, provided together with BTX-A. There were three published investigations in total; but the only study focusing on the upper limb involved people with no active UL function. In conclusion, at the time of writing, there did not seem to be any evidence to indicate which form of additional treatment would be most effective to improve arm function in people with UL spasticity after stroke.

In order to answer the question as to which intervention would be most effective to improve functional activity involving the affected upper limb after stroke, the next section of this literature review will undertake a critical appraisal of the evidence supporting a range of different therapeutic strategies, used in neurological physiotherapy.

1.5 REHABILITATION FOR UPPER LIMB ACTIVITY LIMITATIONS AFTER STROKE

1.5.1 INTRODUCTION

The purpose of this section of the literature review is to provide a critical appraisal of the evidence, pertaining to the efficacy of a range of rehabilitation strategies that aim to improve arm function after stroke. The findings from this review will inform the therapy programme as part of a feasibility RCT, where the effects of a complex intervention including botulinum toxin type-A on spasticity and functional activity involving the upper limb will be explored[1]. The focus will be on treatment strategies aimed at improving activity, whilst those designed to reduce impairments will be omitted.

Several reviews on upper limb rehabilitation after stroke have been published (Richards and Pohl 1999; van der Lee *et al.,* 2001; Hiraoka, 2001; Woldag and Hummelsheim, 2002; Smith, 2004, Barreca *et al.,* 2003; Platz, 2003), whilst a number of more generic reviews on stroke rehabilitation also included the upper limb (Ernst, 1990, Duncan, 1997; Kwakkel *et al.,* 1999a; Pomeroy and Tallis, 2002; Teasell *et al.,* 2003; Steultjens *et al.,* 2003; van Peppen *et al.,* 2004; Baer and van Wijck, 2005).

The comprehensive, systematic review of the effects of physiotherapy on function after stroke by van Peppen *et al.* (2004) found no evidence to support the use of retraining sensory integrity of the upper limb (Yekutiel and Guttman, 1993), stretching (Carey 1990), splinting (Poole *et al.,* 1990; Langlois *et al.,* 1991; Rose and Shah 1980; McPherson *et al.,* 1985), transcutaneous electrical nerve stimulation (Tekeoglu *et al.,* 1998; Conforto *et al.,* 2002; Sonde *et al.,* 1998, 2000), or repetitive strengthening exercises (Bütefisch *et al.,* 1995; Bourbonnais *et al.,* 2002) in order to improve function. Further, the review also found insufficient evidence for the use of exercise, aimed at improving dexterity (Kwakkel *et al.,* 1999b; Lincoln *et al.,* 1999; Sunderland *et al.,* 1992; Gelber *et al.,* 1995; Feys *et al.,*

[1] Some of this material was published as part of a general chapter on physiotherapy after stroke (Baer and van Wijck, 2005, Appendix 6)

1998; Rodgers *et al.,* 2003) and ADL (Logigian *et al.,* 1983; Jongbloed *et al.,* 1989; Kwakkel *et al.,* 1999; Lincoln *et al.,* 1999; Sunderland *et al.,* 1992; Gelber *et al.,* 1995; Werner *et al.,* 1996; Feys *et al.,* 1998; Rodgers *et al.,* 2003). These findings reflected results reported in an earlier review by Teasell *et al.* (2003). Interestingly however, although Feys *et al.* (1998) did not find any significant differences in terms of functional upper limb activity between a group of acute stroke patients, engaged in repetitive stimulation of the affected arm using a rocking chair and a control group, 5-year follow-up data revealed significantly greater gains in arm function in the stimulation group, compared to the control group (Feys *et al.,* 2004. Particularly noteworthy was the finding that the treatment appeared to be most beneficial for the most severely affected patients in terms of their initial motor deficit. It was postulated that in this group, intensive afferent stimulation may prevent detrimental cortical neuroplastic changes from taking place, but that the repetitive, stereotypical nature of the stimulation was not beneficial to foster further functional improvement in patients with better arm function recovery.

Overall, however, the finding by van Peppen *et al.* (2004) regarding the effects of exercise on upper limb function is surprising, since the same review found strong evidence for interventions involving task-specific training to improve lower limb strength, balance and gait. This suggests that some of the upper limb exercise protocols may not have been sufficiently task-specific.

Evidence supporting a functional approach also emerged from an interesting RCT by Winstein *et al.* (2004), which compared additional upper limb functional task practice and additional upper limb strength training with standard care in 64 patients in the subacute stage after stroke in terms of upper limb function and a composite isometric torque measure. The results showed that the two additional intervention strategies yielded similar results and were significantly better than the standard care group at immediate follow up. At 9 month follow-up, there were no significant differences between any of the three groups, but a sub-analysis of the less severely affected participants indicated that those in the functional task practice group had overtaken those in the strength training group in terms of isometric torque measures, while there was also a trend for better upper limb motor function in this group. This study highlighted the benefits of additional upper limb training (which

amounted to 20 hours over 4 weeks) early after the acute event and also made a compelling argument for embedding tasks in a functional context.

The efficacy of task-specific upper limb practice was compared with progressive-resistive exercise (PRE) in a pilot RCT by Thielman *et al.* (2004), involving 12 patients who were mainly in the chronic stage after stroke. Those with high-level upper limb function at the start of the study did not seem to improve on any of the outcome measures (i.e. upper limb function and 2D kinematics of upper limb trajectories) regardless of the type of intervention, but a sub-analysis of those with low-level upper limb function showed the superiority of task-specific practice over PRE in terms of function and hand path trajectory. The study was limited by the small number of participants (i.e. three in each group), whilst follow-up was carried out one occasion only, which may not have addressed long-term retention. However, this study adds to existing evidence to suggest that task-specific practice may be more effective than strength training *per se*.

The importance of the functional relevance of intervention also emerged from systematic reviews pertaining to occupational therapy. Preliminary results from a meta-analysis by Langhorne and Legg (1999), as well as a systematic review by Steultjens *et al.* (2003) indicated that comprehensive occupational therapy, as well as more specific strategies concentrating on skills, yielded positive and significant improvements in ADL.

Taken together, the evidence from a number of reviews on the effects of rehabilitation after stroke converges on two key ingredients that appear to be most successful in promoting function, i.e. task-orientated training (or task-specific practice) and training intensity (Duncan, 1997; Richards and Pohl, 1999; Kwakkel *et al.,* 1999a; van der Lee *et al.,* 2001b, 2003; Hiraoka, 2001; Woldag and Hummelsheim, 2002; Pomeroy and Tallis, 2002; Barreca *et al.,* 2003; Platz, 2003; van Peppen *et al.,* 2004). This raises two main questions: 1) what does "task-specific" practice actually mean? and 2) how intensive is "intensive training"? The first question will be addressed below, while the second will be dealt with in section 1.5.3.

1.5.2 TASK-SPECIFIC PRACTICE FOR IMPROVING UPPER LIMB ACTIVITY AFTER STROKE

1.5.2.1 Task-specific practice: defining the concept

Although the concept of task-specific practice (or task-orientated training) may be understood intuitively, few authors have actually defined it. In this thesis, the term "task-specific practice" will be used. Based on the definition of task-orientated practice from Shumway-Cook and Woollacott (1995: p. 461[2]), task-specific practice is defined in this thesis as:

> *"a therapeutic strategy, based on the systems theory of motor control, designed for patients to acquire proficiency in functional skills through practising specifically those skills."*

The systems theory of motor control, originally developed by Nikolai Bernstein (1967), postulates that motor control emerges from an interaction between the individual, the task and the environment (Shumway-Cook and Woollacott, 1995), which is illustrated in fig. 1.6

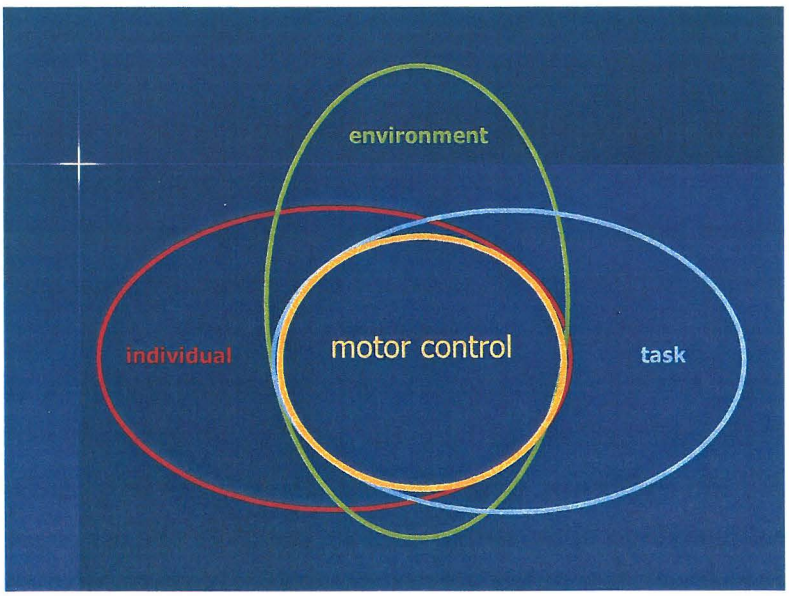


Figure 1.6
Motor control emerging from an interaction between the individual, the task and the environment (redrawn from Shumway-Cook and Woollacott, 1995).

[2] According to Shumway-Cook and Woollacott, task-orientated practice may be defined as : *"a therapeutic approach to retraining the patient with movement disorders, based on a systems theory of motor control"* (1995: p. 461).

Based on this definition, a range of treatments may be labelled as "task-specific practice"; namely the more contemporary interpretation of Bobath, the Motor Relearning Programme, Constraint Induced Therapy (CIT, also known as Forced Use), Bilateral Arm Training, Arm Ability Training and other interventions revolving around the acquisition of specific tasks. In addition to physical practice, some treatments include mental practice, i.e. learning through mentally rehearsing a task without producing observable output. Each of these types of interventions will be discussed in the following sections.

1.5.2.2 Bobath

The "Bobath" approach, developed by Berta and Karel Bobath is probably the most widely practised approach by physiotherapists in neurological rehabilitation across many countries (Nilsson and Nordholm, 1992; Carr *et al.,* 1994; Sackley and Lincoln 1996; Davidson and Waters 2000; Lennon *et al.,* 2001; Pomeroy and Tallis 2002). According to the Bobaths, the CNS is in control of the "normal postural reflex mechanism" and responsible for normal postural tone, reciprocal innervation and automatic movement patterns (Bobath and Bobath 1954, 1964; Bobath, 1971). Consequently, a lesion of the upper motor neurone was thought to result in a release of "lower patterns" of activity from "higher inhibitory control", which was expressed in abnormalities in postural tone (Bobath, 1971). Accordingly, the original aim of this approach was to *prepare* the patient for functional activity by inhibiting "abnormal" movement patterns and facilitating more "normal" movement, thereby enhancing the quality of movement (Bobath 1969, 1990). This was primarily achieved by providing the patient with the sensation of more normal movement through skilful handling by the therapist and by placing the patient in so-called "reflex-inhibiting postures" to reduce spasticity (Bobath and Bobath, 1957). However, carry-over into functional abilities turned out to be limited (Mayston, 1992). As the approach developed, Mayston (2002) stated that the traditional focus on spasticity and righting and equilibrium reactions was considered to be outdated. With the initial emphasis on quality of movement shifting towards the optimisation of function, some degree of compensatory strategies and a reduction in movement quality were becoming more acceptable (Edwards, 2002). In their working

document, the International Bobath Instructors Training Association (IBITA) [http://www.ibita.org/] defined the Bobath concept as follows:

> *"a problem-solving approach to the assessment and treatment of individuals with disturbances of function, movement and postural control due to a lesion of the central nervous system."*

They expressed their focus on function by stating that:

> *"Intervention seeks solutions for motor behaviour which interferes with successful performance of an activity. Treatment strategies address underlying impairments, task-specific components of posture and movement, the functional activity itself and its integration into participation in relevant situations in daily life. Cognitive, emotional and behavioural factors are addressed in order to enable the individual to engage in task-related problem-solving." (ibid)*

However, despite claims published earlier (Mayston 1992), that the Bobath approach had become more functional and problem-orientated, Lennon *et al.* (2002) suggested that more emphasis could be placed on the practice of *actual functional tasks,* rather than on the *preparation* of function.

While the Bobaths made a significant contribution to the neurological physiotherapy, the approach has been criticised on a number of points, including the lack of clear definitions (e.g. "tone", VanSant, 1991). The assumption that physical exertion would exacerbate spasticity has also been challenged by more recent data (Bütefisch *et al.,* 1995; Badics *et al.,* 2002; Morris *et al.,* 2004). Furthermore, evidence from a review of 15 studies (including six RCTs) investigating the efficacy of this approach concluded that there was no evidence to support it (Paci, 2003). Additionally, much of the evidence was affected by methodological problems, i.e. possible confounding by spontaneous recovery, heterogeneity in patient populations, a lack of information about therapeutic input and diversity in assessment procedures. Interestingly, Paci (2003) noted a lack of congruency between an important goal of Bobath therapy, i.e. obtaining more normal movement (Lennon and Ashburn, 2000) and outcome measures, which concentrated on actual function. Recommendations from Paci's review (2003) included the need to employ outcome measures that reflect the treatment aims and consider the cost-effectiveness of the approach. He also emphasised that the Bobath approach needed to be further defined and standardised. This criticism has been supported by other authors, who pointed out the lack of up-to-date literature on the specifics of

the therapeutic input (Davidson and Waters, 2000; Mayston 2002), which has resulted in diverging interpretations of "the Bobath approach". Although this problem is beginning to be addressed, it still requires further work (Lennon and Ashburn, 2000; Paci 2003).

1.5.2.3 Motor Relearning Programme

The Motor Relearning Programme (MRP) for Stroke (Carr and Shepherd, 1987, 1989, 1998, 2000, 2003) provides guidelines for a training programme, based on evidence from a range of scientific disciplines. The main assumption underpinning this approach is that regaining activities of daily living (ADL) after stroke requires a re-learning process, which is thought to be similar to that in non-impaired people (Carr and Shepherd, 1998). Normal movement is thought to consist of so-called essential components (i.e. the invariant kinematics of an activity), which enable the performance of many different activities (Carr and Shepherd, 1987). Training involves task-and context –specific activities.

The aims of the MRP are to re-learn every day functional tasks (Carr and Shepherd, 1998) while soft tissue extensibility, muscle strength as well as fitness are addressed. The main role of the therapist is to facilitate the motor re-learning process by identifying the patient's problems, analysing movement through observation and comparing this with normal movement. The therapist also identifies those critical components that are thought to be "missing" or poorly controlled. Carr and Shepherd (2000) defined "critical components", which tend to be invariant across subjects and conditions, as:

> *"observable joint angular displacements and linear paths of body parts (e.g. the shoulder path in moving from sit to stand, ...or the hand path in reaching to an object) developed from biomechanical studies and replicated under different conditions"* (pp. 44-45).

Using goal setting, instruction, feedback and manual guidance, the therapist teaches the patient to perform these so-called "missing components". These are then practised, followed by training of the task in a more functional context to promote transfer. The patient is encouraged to practice relevant tasks extensively, not only under supervision of the therapist but also independently, using both physical and mental practice in a variety of environments.

The efficacy of this approach has been evaluated in a small number of studies. Dean and Shepherd (1997) focused on sitting balance during reaching in a RCT involving 20 chronic stroke patients. Patients in the experimental group trained reaching tasks with the non-affected arm beyond arm's length, while they focused on loading the affected lower limb. In contrast, the control group practised cognitive-manipulative tasks involving the non-affected side within arm's length only. The results suggested that training led to an improvement of the skills that had been practised, but not of skills that had not been practised. One limitation was that only one post-test was carried out at an unspecified time after treatment had finished and therefore it was not entirely clear what the longer-term effects of this type of intervention were.

In a later RCT, Dean *et al.* (2000) piloted a circuit-training programme for 12 chronic stroke patients, designed to improve locomotor-related tasks. The experimental group trained lower limb activities, whilst the control group trained upper limb activities only. The duration and frequency of the programme were identical for both groups. The results indicated that circuit training involving functional tasks was feasible for chronic stroke patients and that the benefits were specific to the type of training received. Despite the important finding that training in the chronic stage after stroke yielded functional benefits, even at two month-follow up, these findings need to be interpreted with caution, as the authors acknowledged that blinding had been insufficient. Additionally, the study could be criticised by failing to analyse the – considerable - differences between the two groups at baseline, which may have influenced the results. More importantly, given the specificity of learning hypothesis[3], it is unlikely that the upper limb training would have carried over into lower limb function and therefore the design of the study, in terms of evaluating transfer, was perhaps rather naive.

Monger *et al.* (2002) reported the effects of a task-specific practice programme for six chronic stroke patients to improve sit to stand. The value of this study is limited, however, by the omission of a control group, the small sample size and the inclusion of only one post test at an unspecified point in time.

[3] The specificity of learning hypothesis (e.g. Barnett *et al.,* 1973, Proteau *et al.,* 1992) predicts that skill acquisition is enhanced when conditions of practice match those during retrieval in terms of movement components and the environment.

One of the strengths of the MRP approach is that it incorporated current scientific evidence at a time when the Bobath approach appeared to be primarily based on outdated information and dogma. However, an important limitation of the MRP is that it may only be appropriate for a limited sub-population of stroke patients, since with its emphasis on independent practice, it is unlikely that more severely affected patients would be able to participate – although this still requires to be established more formally. From a theoretical perspective, a question mark could be placed at Carr and Shepherd's (2000) interpretation of "critical components". For example, it is arguable whether the "hand path in reaching for an object" (p. 45) is invariant across situations - even within a subject - as the number of permutations for controlling the various degrees of freedom involved in reaching for different objects at different locations is considerable (Bernstein, 1967).

More fundamentally, the MRP approach is based on principles of skill acquisition, derived from research with non-impaired people. One pertinent question is therefore whether methods used to optimise motor learning in people with a CNS lesion are identical to those in non-impaired subjects (Carr and Shepherd, 1987, 1998). Carr and Shepherd (1998) acknowledged that there were bound to be anatomical and functional differences between learning a new task using a non-lesioned brain and relearning a task formerly mastered using a lesioned brain, but their approach appears to be based on the assumption that these situations are equivalent. On a behavioural level, this appears to have face validity. However, although there is evidence that a stroke involving the sensorimotor cortex may affect performance, but not the ability to learn upper limb motor skills Winstein *et al.* (1999), a cohort study by Poole (1998) investigating the acquisition of a functional task (i.e. tying a shoe lace with one hand) showed that patients with a left-sided stroke and apraxia had considerable difficulty with this task, compared to patients with a left-sided stroke without apraxia and non-impaired controls. This indicates that it cannot be simply assumed that the ability to (re)learn functional tasks after a stroke is intact in all patients. It is clear that skill acquisition processes in people with a CNS lesion has hardly been investigated (Pollock, 1998) and requires further investigation.

1.5.2.4 Constraint Induced Therapy

Constraint Induced Therapy (CIT) or Forced Use of the upper extremity in hemiplegic patients is a therapeutic technique in which the more affected side is involved in daily training for prolonged periods of time over consecutive weeks while the non-or less affected upper limb is constrained by a mitt or sling for up to 90% of "waking hours" (Taub and Uswatte, 2003). This forces the patient to use the more affected upper limb in functional activities for most part of their day. The idea for CIT is based on observations of monkeys after experimentally induced deafferentation (Ogden and Franz 1917, cited in Taub *et al.*, 1993; Taub 1980). Following this procedure, it was observed that the animals avoided using their affected arm. After their non-affected upper limb had been constrained, it was noted that the animals started to use their affected upper limb again. Taub (1980) suggested that non-use of the affected upper limb is, at least to some extent, the result of a conditioning process. In their synthesis of research on CIT, Taub and Uswatte (2003) explained how three processes could lead to so-called "learned non-use": punishment for using the affected limb (e.g. discomfort, loss of food objects), positive reinforcement for using the non- or less affected side and cortical reorganisation following the natural or experimental lesion, which involved shrinkage of the cortical representation area for the affected limb.

The first report on Constraint Induced Therapy (CIT) or Forced Use for humans was published by Ostendorf and Wolf in 1981. This was a single case experimental study of a hemiplegic patient, which showed a number of promising findings. This was followed by a number of group studies of patients with hemiplegia (e.g. Wolf *et al.,* 1989; Taub *et al.,* 1993; van der Lee *et al.,* 1999; Miltner *et al.,* 1999). Results generally appeared to be positive, ranging from small improvements that were maintained at one year follow-up (van der Lee *et al.,* 1999), to considerable improvements in observed and self-reported arm function, which were maintained at six-month follow-up (Miltner *et al.,* 1999). A limitation of the study by Miltner *et al.* (1999) was that it did not involve a control group, whereas the study by van der Lee *et al.* (1999) was an RCT that involved a carefully matched control intervention. Most research on CIT has been conducted with chronic stroke patients; less is known about the efficacy of this technique with (sub)acute patients, although a study

by Dromerick *et al.* (2000) involving patients within two weeks of stroke onset, also showed positive effects of CIT in terms of improved dexterity and dressing, whilst no adverse reactions were encountered. One limitation was that post-testing only took place directly after the end of the intervention, leaving longer-term effects unexplored.

Research on CIT has sparked an interesting line of enquiry in neurological rehabilitation, associating changes at a behavioural level with those at a neuronal level. Using neuro-imaging techniques, a number of studies have provided evidence of the neuroplastic changes occurring as a result of CIT (Taub *et al.,* 1993, 1999). For example, Liepert *et al.* (2001) used focal transcranial magnetic stimulation (TMS) to investigate changes in motor output areas of the paretic m. abductor pollicis brevis following CIT. Associated with improvements in dexterity, increased motor cortex excitability was found, as well as recruitment of adjacent brain areas within the affected hemisphere. Using functional magnetic resonance imaging (fMRI), Levy *et al.* (2001) found an increase of activation nearer the lesion site in two stroke patients as a result of CIT. Although such studies were typically small and may have lacked a control group, the results were nevertheless groundbreaking. Further supporting evidence is discussed in the interesting review on CIT studies, published by Taub and Uswatte (2003).

CIT may not be suitable for all patients, however. Firstly, it is important to note that most studies excluded patients with less than some degree of active wrist movement. Hence, it is unlikely that this approach would be appropriate for more severely affected patients. Secondly, a survey of patients and therapists revealed that many regard CIT as too demanding, while it was also suggested that it is unethical to restrain patients in such a manner (Page *et al.,* 2002[a]). Furthermore, the costs of therapy are not inconsiderable, as the intervention requires prolonged therapist-patient interaction. To render CIT more feasible, Page *et al.* (2001[b], 2002[c]) devised a modified CIT (mCIT) protocol, which involved a 10-week programme of 30 minutes physical and 30 minutes occupational therapy, given 3 x per week, while patients were wearing a sling and mitt on the affected upper limb 5 days per week for 5 hours, during a period where the arm was used frequently. Results from these feasibility studies suggested that this mCIT programme was effective in terms of improving arm function and was also well received by patients and therapists.

Further larger-scale studies with longer follow up time are now required to corroborate these findings.

Although several reviews on upper limb therapy identified CIT as an effective intervention (van der Lee *et al.,* 2001[b]; Hiraoka 2001; Barreca *et al.,* 2003; van Peppen *et al.,* 2004), critical comments have been placed at the extent and robustness of the evidence (Dromerick, 2003; van der Lee, 2003). In his editorial, Dromerick (2003) highlighted the absence of multi-centre studies, whilst only a small number of RCTs had been conducted, only two of which involved more than 20 subjects and included a separate control group. A systematic review of four RCTs by van der Lee (2003) showed that, although all studies reported improvements in upper limb function, the effects on activity limitations were absent in two studies. Similarly, van Peppen *et al.* (2004) found significant effects on some measures of upper limb function, but benefits in terms of actual use of the affected arm in every day life were absent. Additionally, the amount of time spent with the therapist during CIT is considerably longer than in most UL intervention studies, which may act as a powerful placebo for which future RCTs will need to control. Taken together, Dromerick cautioned against the "*extravagant fanfare*" (p. viii) that accompanied CIT, recommending that it was time for well-designed multi-centre studies.

1.5.2.5 Arm Ability Training (AAT)

For patients with stroke or traumatic brain injury (TBI) with good but not perfect recovery of arm function, Platz developed the evidence-based Arm Ability Training (Platz *et al.,* 1999, 2001; Platz, 2004). The concept "motor abilities" refers to:

> *"different independent sensorimotor capabilities that together support a wide range of arm activities"* (Platz *et al.*, 2001: p. 961).

Examples of arm motor abilities are dexterity, steadiness, precision, speed of isolated hand and finger movements and the ability to use on-line visual input to control movement, which have been shown to be deficient in highly functioning stroke patients (Platz *et al.,* 2001). The underlying assumption is that training these basic abilities would transfer into improved performance in a range of different situations. The programme has a standardised structure, although the workload is tailored to the level of each patient. Training concentrates on eight tasks (fully

described in Platz *et al.* (2001): hitting targets with a stylus, finger tapping, circle cancellation, coin turning, maze tracking, picking up nuts and screwing them onto bolts, placing small wooden objects on top of each other, and placing water-filled jam glasses on top of each other. Practice is varied and focuses on improving general performance, as well as speed and accuracy, with feedback being provided about the outcome of the task (knowledge of results) to enhance motivation and learning.

The efficacy of this approach was tested in a RCT involving 45 patients with stroke and 15 with TBI (Platz *et al.*, 2001). The trial compared the effects of a daily AAT schedule with or without feedback, which was additional to standard rehabilitation, and no AAT. AAT consisted of 15 training units; one per weekday for three consecutive weeks. Each unit would take up a maximum of 32 minutes, but this decreased as the patient became more efficient. The outcomes were recorded in terms of time required to complete items on the TEMPA test[4], as well as speed and accuracy of aiming movements, recording on a digitizing tablet. The results showed that patients participating in AAT improved significantly compared to the control group in terms of the time needed to complete the TEMPA tasks, both at immediate testing and one year follow up. Clinically, this translated into an 8% reduction in time for the control group, compared to an 18% reduction in the AAT groups. In terms of the kinematics of aiming movements, significantly greater speed was achieved in the ballistic component of the movement in those receiving AAT, but not in the homing-in phase, compared to the control group. Taken together, the authors interpreted the results to indicate that AAT may improve the ballistic component in motor function. Augmented feedback did not have any significant impact, which could be explained if participants were already aware of their performance. Side effects included shoulder pain or discomfort in five of the 40 patients taking part in AAT.

The contribution of AAT is that it provides a therapeutic programme for patients with stroke or TBI, who have achieved good, but not perfect upper limb recovery, which may limit their return to work. It is based on relevant evidence from the motor control literature and its description of the therapeutic input is considerably more detailed than most upper limb therapy programmes. The rationale for selecting

[4] Test Évaluant le performance des Membres supérieurs des Personnes Agées (Desrosiers J, Hébert R, Dutill, É. Bibliothèque Nationale the Québec, 1991.

tasks for the intervention programme, which is based on factor analysis of motor performance in non-impaired people is also of interest. However, one could question to what extent this approach is patient-centred, as there was no evidence to suggest that patients had been involved in the selection of tasks for their training programme, or asked for their opinion regarding the relevance of the programme for their ADL, which is not immediately clear for some of the tasks. More fundamentally, given the specificity of learning hypothesis (Proteau *et al.*, 1992), the premise that training of basic sensorimotor capabilities would transfer into a range of tasks is questionable. In actual fact, AAT involves the training of tasks, as opposed to training sensorimotor capabilities *per se*, with each of the tasks drawing on a range of capabilities. Finally, whether improvements in ballistic behaviour are useful in actual ADL remains to be determined.

1.5.2.6 Bilateral Isokinematic Training (BIT)

Bilateral Isokinematic Training (BIT) is a method for re-educating the affected upper limb, developed by Mudie and Matyas (Mudie and Matyas, 1996; 2000). It employs bilateral isokinematic movements, which are defined as:

> *"spatiotemporally identical movements performed bilaterally but with each limb independently* (Mudie and Matyas 2000: p. 24)

Typical examples of tasks are block placing and peg targeting (Mudie and Matyas, 1996, 2000). The rationale for this method is based on the theory that BIT facilitates recruitment of corticomotor neurone pools, which are depleted following a stroke (Turton *et al.,* 1993), as well as their integration into task-specific neural networks. Based on neurophysiological data, two key mechanisms were proposed, thought to mediate the effects of BIT (Mudie and Matyas, 2000); firstly, by coupling the non-affected with the affected limb, the undamaged hemisphere generates a "template" for action that is relayed, via the corpus callosum, to the damaged hemisphere and this is thought to facilitate the reorganisation of neural networks within the affected hemisphere. Secondly, new neural networks may also be developed, since BIT releases the inter-hemispheric inhibition that is normally in place when a unilateral task is undertaken. Mudie and Matyas (2000) proposed that new pathways could involve spared ipsilateral pathways from the damaged hemisphere, as well as direct and indirect ipsilateral pathways from the non-affected hemisphere. However, a

more recent study by Lewis and Byblow (2004) indicated that the precise neurophysiological mechanisms operating during this form of intervention are still unclear. Luft *et al.* (2004) explored changes in brain activity using fMIR in those patients who showed significant improvements (n=6 out of 9) following an intervention of BIT combined with rhythmic cuing. Their findings indicated increased recruitment in the sensorimotor areas of the non-affected hemisphere as well as the ipsilateral cerebellum. In those who did not improve arm function, these changes were absent.

Most studies on the effects of BIT have been non-RCTs (Mudie and Matyas, 1996, 2000; Whitall *et al*, 2000; McCombe *et al.,* 2004; Lewis and Byblow, 2004). A RCT by Cauraugh and Kim (2002) explored the combination of BIT with EMG-triggered neuromuscular stimulation with chronic stroke patients and compared this with unilateral training together with the same electrical stimulation and a control group that only performed the unilateral wrist and fingers extension movements. In terms of function, significantly more improvement was found on the Box and Blocks test in the first group than in the other two, while the second group gained more benefit than the third. Although combining the two techniques presented an interesting development, its longer term effect needs to be further explored, since it was not stated when the single post test was carried out.

Although BIT may be labelled as a task-specific form of practice, the actual ecological validity of tasks varied between studies[5]. Whitall *et al.* (2000) and Luft *et al.* (2004) used a device on which patients performed repetitive, rhythmic pushing- and pulling movements in the transverse plane, whereas Lewis and Byblow (2004) used more functional tasks, including block placement and drinking – although this was only simulated. It is plausible that the functional relevance of the tasks had an effect on the outcomes of the intervention and therefore future studies will need to take this factor into consideration. A further question is to what extent bilateral practice carries over into unilateral or bilaterally different tasks – would there be a need for patients to learn to *un*couple the two limbs following BIT? It is possible that BIT could be most useful in the initial stage in the skill acquisition process, when patients need to acquire the "image" of the activity, or when insufficient recruitment

[5] In an RCT involving hemiplegic patients with very severely affected upper limbs with no active function, Mudie and Matyas (2001) used isometric contractions of shoulder abductors and wrist extensors.

of the required cortical motor neurone pools constitutes the main problem (Mudie and Matyas, 2000). The possibility that continuing BIT beyond this initial stage may yield no, or even negative carry-over to non-bilateral tasks, would need to be determined in future work. Taken together, BIT promises an interesting line of research, which will contribute to the body of knowledge pertaining to motor control problems at both the neurophysiological and behavioural levels of analysis.

1.5.2.7 Other forms of task-specific practice

A number of studies investigated the effects of treatment techniques, which did not carry a formal "label", but nevertheless fitted the definition of task-specific practice.

A highly original and innovative approach was devised by Altschuler *et al.* (1999), who used a randomised controlled cross-over trial to explore the effects of bilateral arm movements, while the image of the non-impaired upper limb was superimposed onto that of the impaired upper limb by means of a mirror. Nine people in the chronic stage after stroke practised bilateral arm movements, progressing from proximal to distal, for 15 minutes per day, twice per day, six days per week for four weeks, while they either watched their affected arm through transparent plastic during one phase of the trial or the image of their non-affected arm reflected by a mirror during the other phase. The results were favourable, with patients expressing positive experiences and blinded assessors noting a greater number of improvements in the condition featuring the mirror. The authors suggested that the normal visual image from the non-affected arm may have improved motor control by providing a substitute for the decreased afferent input from the affected limb. Further studies that employ validated outcome measures for upper limb function and consider long term carry-over into functional UL activity are warranted, given the content of the therapeutic programme that – at least from its brief description - appeared to feature mere movement. Nevertheless, the initial results from this study were promising.

Task-specific practice is not necessarily beneficial however, with a study by Woldag *et al.* (2003[a]) showing no differential effects of additional repetitive training of complex upper limb movements, compared to standard occupational therapy and

physiotherapy. Twenty-one stroke patients between two and 46 weeks after the acute event were included. The upper limb training programme, which was administered in addition to standard therapy, consisted of two tasks, i.e. picking and placing a mug over a standard distance and simulated sawing movements, for 10 minutes per task, twice per day, five days per week for four weeks. No significant differences were found in terms of arm function, grip force, rapid isotonic wrist extension or 3D upper limb kinematics, between the phase involving standard therapy and the phase involving the additional training. Rather than concluding that repetitive training of complex upper limb movements is not useful, as the authors suggested, one could question the ecological validity of the tasks included. Additionally, since the type of practice schedule was not mentioned, it is possible that the strategy may not have been optimal.

Disappointing results of task-specific practice were also reported by Turton and Butler (2004) who investigated the effects of repetitive hand function training in seven single case design experiments with people in the chronic stage after stroke. Their programme consisted of four tasks, i.e. isometric pinch, isotonic pinch, isometric and isotonic rotation of handgrips, using a computer-based training package. Practice, which focused on speed and accuracy of performance, was organised in four blocks of 80 trials each for approximately 20 minutes per day, twice daily for four weeks. Each subject completed between 5760 and 18560 tasks in total. Outcomes were evaluated using the ten hole peg test and a timed nuts and bolts test. Changes at a neurophysiological level were also assessed by means of EMG responses to transcranial magnetic stimulation. Despite the (somewhat surprisingly) high compliance, significant effects as a result of the training were found in two subjects only, while there was no evidence of any neurophysiological changes. The authors acknowledged that the lack of efficacy of their training programme could be attributed to the repetitive and stereotypical nature of the movements being practised. The functional value of training speed and accuracy of isometric grip strength and turning a limited set of knobs for ADL is indeed questionable.

In summary, the studies by Woldag *et al.* (2003[a]) and Turton and Butler (2004) highlight that repetition of movement *per se* may not be beneficial, but that the ecological validity of the tasks needs to be considered additionally.

1.5.2.8 Mental practice

Mental practice (MP), also referred to as "movement imagery" or "covert practice", involves the cognitive rehearsal of movement in the absence of overt activity (Martin *et al.,* 1999 for a review). It is used extensively in sports and dance to enhance performance (Magill, 2001). Although the integration of mental practice in rehabilitation has been advocated by numerous authors (e.g. Decety, 1993; Van Leeuwen and Inglis, 1998; Jackson *et al.,* 2001), there are very few empirical studies on the effectiveness of mental practice in people with CNS lesions. Several case and small scale pilot studies have been reported using mental practice to enhance upper limb function (Yoo *et al.,* 2001; Stevens and Stoykov, 2003; Crosbie *et al.,* 2004; Dijkerman *et al.*, 2004). Effects of mental practice on lower limb function were reported in a case study by Jackson *et al.* (2004), while Malouin *et al.* (2004) used a cohort study to explore the effects of MP on a mobility task. Liu *et al.* (2004) reported a RCT using mental practice for a range of ADLs, but given the poor descriptions of the content of many of the tasks (e.g. "see the doctor"), its relevance for this thesis was unclear and therefore this RCT will not be further discussed.

A systematic review on upper limb rehabilitation by Barreca *et al.* (2003) indicated a significant effect of mental practice together with occupational therapy in two RCTs. The first RCT by Page (2000) was a pilot study involving 16 chronic stroke patients, who were randomised to a four-week programme of either OT or OT together with mental practice. OT was provided to both groups for 30 minutes, three times per week for four weeks. In addition to each session, the experimental group took part in 20 minutes of mental practice with tape-recorded instructions, of which 10 minutes were spent imagining using the affected arm in tasks, practised during the preceding OT session. The control group also listened to an audio tape for the same length of time, but this provided general information about stroke only. The results showed that both groups improved at follow-up, but the OT plus mental practice group demonstrated significantly greater improvements in arm motor function, assessed on the Fugl-Meyer test, than the OT-only group. However, since only one post-test had been carried out, longer term effects could not be ascertained.

In a following RCT, Page *et al.* (2001[b]) carried out a similar study involving 13 patients between 2 -11 months after stroke. Physiotherapy and OT were provided for one hour, three times per week for six weeks, after which patients listened to a ten minute audiotape. The content of the tapes for the experimental and control groups was similar to the previous study. The results supported those from the previous pilot study by Page (2000), indicating that patients using mental practice achieved considerable improvements that were not only statistically, but also clinically relevant in terms of impairments (Fugl-Meyer: +13.8 out of 66 points) as well as activity limitations (i.e. Action Research Arm Test: +16.4 out of 57 points). In contrast, improvements in the control group were negligible (i.e. Action Research Arm Test: +0.7 out of 57 points, Fugl-Meyer: +0.7 out of 106 points). The use of parametric statistics on ordinal level data could be questioned, but the difference in magnitude of the improvements between both groups was nevertheless clearly apparent. One limitation of this study was the variability in time post-stroke, which may have confounded the results, but the findings were certainly promising.

In an interesting study with eleven chronic stroke patients, discharged from outpatient therapy as they were perceived to have reached a "plateau", Page *et al.* (2005) studied the effects of mental practice on arm function (using the Action Research Arm Test: Lyle, 1981) as well as self-reported arm use during ADL (using the Motor Activity Log or MAL, see Uswatte *et al.,* 2005). A randomised controlled case study design was used with two pre-tests and one post-test. Treatment consisted of two 30-minute ADL training sessions per week for six weeks, followed by 30 minutes of mental practice, including 20 minutes of mental practice of the same tasks undertaken during ADL training. The control group followed the same ADL training and then listened to a 30-minute audio tape designed to enhance relaxation. Interestingly, despite ARAT scores suggesting only moderately affected arm function at baseline, the MAL indicated that the actual use of the affected arm in ADL was almost negligible in both groups. Immediately after treatment, notable improvements were found in both the ARAT and the MAL in favour of the mental practice group, but longer term effects were not ascertained. Given that patients' arm function had been stable prior to the study, the authors attributed the difference in treatment effects between the two groups primarily to the mental practice

component. Importantly, these surprising results led Page *et al.* (2005) to question the assumption of the so-called "plateau" of recovery after stroke.

Although many aspects of mental practice still require further research, an understanding of the effects of this type of intervention has been greatly facilitated by neuroimaging and techniques such as transcranial magnetic stimulation (Jeannerod and Frak, 1999), which will be discussed in section 1.5.2.8.

The advantages of mental practice are that it is generally well tolerated, easy to perform and - provided that adequate instructional material is available and the patient is able to use this independently - it can be undertaken out with therapy time. Given the fact that practice time is scarce in most rehabilitation settings, this is an important consideration. A fundamental restriction of this technique, however, is that it is as yet impossible to monitor if and how it is carried out. Additionally, there is little evidence to indicate whether particular brain lesions affect the ability to engage in mental practice. Johnson (2000) reported that many adults retain the ability to use motor imagery following a brain lesion, but cautioned that those with right posterior parietal or left frontal lobe lesions could experience difficulty. At present, however, there is a lack of research to indicate for which patients this learning strategy may or may not be suitable. However, based on clinical reasoning one would expect that, due to the verbal-cognitive content of the instructions that are part of this technique, mental practice may not be suitable for patients with severe attentional or short-term memory impairments and/ or disorders of speech comprehension, but this has not been formally established. The work carried out by Page, 2000; Page *et al.*, 2001[a,b], 2005) suggests that mental practice holds promise for stroke rehabilitation, including for those with chronic arm function problems and warrants further research, especially with respect to long-term retention and carry-over.

1.5.2.9 Electrical Stimulation and Biofeedback

Some task-specific practice strategies include a particular type of technology, e.g. electrical stimulation (ES) or EMG biofeedback, which may be combined in EMG-triggered ES. However, the most recent and comprehensive systematic review by

van Peppen *et al.* (2004) demonstrated that the evidence for the functional effects of ES was limited. Only one RCT applying ES to the wrist extensors in sub-acute stroke patients showed significant improvements in isometric wrist extensor force and a trend for tasks involving selected pick-and place activities to improve, but this was only significant in people with some remaining voluntary wrist and finger control at baseline (Powell *et al.,* 1999). Similarly, van Peppen *et al.* (2004) concluded that there was insufficient evidence for the functional effect of biofeedback, applied to the upper limb. Taken together, the most recent evidence shows limited support for ES and biofeedback and these techniques will therefore not be discussed further.
Robot-assisted training and virtual reality represent emerging technologies, which will be described in the next section.

1.5.2.10 Emerging technologies

Interventions currently in a more experimental stage include virtual reality (e.g. Sisto *et al.,* 2002, Merians *et al.,* 2002; Deutsch *et al.,* 2004), in some cases designed for telemedicine applications (e.g. Gourlay *et al.,* 2000; Piron *et al.,* 2004), or integrated with haptic devices (e.g. Adamovich *et al.,* 2005; Loureiro *et al.,* 2003[6]). A review of virtual environment techniques for motor training in neurological rehabilitation indicated positive results in terms of improvements on learned tasks as well as carry-over into untrained tasks, whilst the technology appeared to be well tolerated (Holden, 2005). The attitudes of patients and therapists regarding the device described by Loureiro *et al.* (2003) were generally positive, although the survey by Coote and Stokes (2003) emphasised the need to involve users in further development of this type of technology.

Robotics, designed for rehabilitation, have come a long way over the last 25 years (see Burgar *et al.,* 2000) and robot-assisted training in stroke rehabilitation has been tested in a number of studies (Krebs *et al.,* 1999; Volpe *et al.,* 1999, 2000; Ferraro *et al.,* 2003; Fasoli *et al.,* 2003, 2004;Hesse *et al.,* 2003[a,b]; Lum *et al.,* 2004; Stein *et al.,* 2004; for an overview see Hesse *et al.,* 2003[a] and Fasoli *et al.,* 2004), although

[6] Loureiro *et al.* (2003) described a system using a haptic interface and virtual reality. visualisation, which was tested as part of an EU collaboration [http://www.gentle.rdg.ac.uk/].

only a few RCTs have been carried out so far. The results from RCTs (Volpe *et al.,* 2000; Lum *et al.,* 2002; Hesse *et al.,* 2005), appear to be promising in terms of measures of impairment, with functional independence also improving in some studies (Volpe *et al.,* 2000; Lum *et al.,* 2002). However, in some investigations, the results may have been confounded by differences in the number of repetitions between different groups (e.g. in a RCT by Hesse *et al.* (2005) this differed by a factor of 10 in favour of the robotics group). Additionally, most training programmes were impairment-focused and given the specificity of training hypothesis, it will be important for future research to investigate long term carry-over from these interventions into more functional activity.

Provided that health and safety requirements are met, these technologies may provide valuable opportunities for patients to relearn perceptuo-motor skills in an enriched, interactive, yet controllable environment with extended scope for independent practice. The optimum patient characteristics and the barriers and opportunities for their implementation in routine clinical practice however, are issues of continuing debate.

1.5.2.11. Efficacy of task-specific practice: behavioural and neuronal explanations

Having evaluated the evidence from clinical trials featuring task-specific practice, it is time to explain its potential impact on functional activity. In this section, explanations will be offered on two different levels of analysis, i.e. the behavioural and the neuronal.

At a behavioural level, task-specific practice is compatible with the specificity of learning principle (e.g. Proteau *et al.,* 1992), which predicts that skill acquisition is enhanced when conditions of practice match those during retrieval in terms of movement components and the environment. This principle, in turn, may be seen as a specific application of the principle of transfer-appropriate processing in general memory theory, which postulates that the congruency between processes involved in encoding and retrieval determine the strength of the memory (Bernstein *et al.,* 2006).

This principle may also be explained at the neuronal level of analysis. The contemporary model of the central nervous system is that of a functionally organised, distributed hierarchical circuit, where information processing occurs in a parallel-distributed manner (Kolb and Whishaw, 2003). The corresponding view of the relationship between the brain and behaviour is that many functions are represented by specific maps in the brain and may be served by more than one neural pathway (Kandel *et al.*, 2000). Firstly, this implies that a particular function is mediated through a specific neural network and that if this function is to be improved, it requires training that targets that specific neural network. Secondly, this view implies the presence of redundancy, which is at the very foundation of rehabilitation. Put simply, redundancy refers to the ability of the brain to recruit intact, surplus substrate in order to recover function (but see Benton and Tranel (2000) for an interesting historical overview of this concept). However, reorganisation of function is not only due to substitution, but also to re-shaping and re-organisation, together known as neuroplasticity[7]. Kolb and Whishaw (2000) outlined three main processes that mediate cerebral reorganisation following brain damage: spontaneous reorganisation, application of behavioural or pharmacological treatment and replacement of lost cells and functions.

In terms of neuroplastic changes, the capability of the adult brain to reorganise itself following injury is widely recognised (Levin and Grafman, 2000; Nudo, 2003[a,b] ; for a review see Johansson, 2000), although the precise mechanisms whereby changes in the somatosensory system occur are not yet fully understood (Ergenzinger and Pons, 2000). Neuroplastic changes may take place at different levels of analysis (e.g. molecular, cellular, and organ, see table 1.6 for an overview), while further changes may take place at the level of the organism as a whole, as well as the organism within its environment.

Following spontaneous recovery after brain damage, early lesion studies in animals showed deleterious changes in cortical maps of affected extremities, with parts of representations of the hand being replaced by those of more proximal limb segments. However, these animals did not receive any training, whereas in subsequent studies where training was provided, these adverse changes did not

[7] Plasticity: from Greek *πλασσειν*: to mould (Chambers English Dictionary, 1990)

occur (Nudu, 1998; Nudo *et al.,* 2000). This evidence has been taken to support the instigation of rehabilitation following brain damage.

Brain reorganisation that supports functional recovery is most likely to occur within local cortical circuits that have been affected (directly or indirectly) by the brain lesion, with the likelihood of finding evidence for reorganisation being greatest in the efferent projection neurons, i.e. the pyramidal cells (Kolb and Whishaw 2000). This observation has important implications for rehabilitation: with cortical reorganisation being confined to local circuits, therapeutic strategies most likely to be effective in driving this neuroplastic process should target those circuits; i.e. through specific activities. Within local areas in the primary motor cortex in rodents (e.g. the hand area), Nudo *et al.* (2000) found that there was no strict topography but considerable overlap in anatomical organisation. This would enable functional reorganisation to take place within each local area and provide an explanation for Kolb and Whishaw's observation of functional recovery mainly taking place within affected local circuits. Neuroplastic changes may go beyond local areas however; Nelles *et al.* (2001) reported that three weeks of task-orientated UL training by severely affected stroke patients led to increased activity, bilaterally in the premotor and contralaterally in the sensorimotor cortex, which was not observed in the control group treated by passive UL movement only.

An interesting observation by Nudo *et al.* (2000, 2003) was that changes in cortical representation of the hand only emerged after the acquisition of new skills, but not after repetitive movement. This is a most important finding for clinical practice and emphasises that neurological rehabilitation should engage the patient in progressively complex skill acquisition, instead of mere repetitive movement.

It is interesting that these findings, which were mainly based on rodent research, are supported by evidence from studies on constraint induced therapy (CIT) in people after stroke (Taub *et al.* 1993, 1999), which was presented in section 1.5.2.4 (e.g. Liepert *et al.*, 2001; Levy *et al.,* 2001; Taub and Uswatte, 2003).

Neuroplasticity is not necessarily conducive to recovery, however; Nudo *et al.* (2000) stated that long-term neuroplastic changes may be *"adaptive, maladaptive or epiphenomenal"*. For example, there are several reports of adverse effects in rodents following rehabilitation that was too intensive too early (see Schallert *et al.,*

2000). Kolb and Whishaw (2000) also found that pathological expansion of cortical connectivity following brain lesions in rats was actually associated with poor recovery. This is a most interesting finding, as it lends further support to the interpretation that spasticity is plasticity gone haywire (cf. Bach-y-Rita, 2000). When activated, exuberant dendritic arborisation and expansion of cortical connections may be expressed, via the pyramidal tracts and henceforth through the final common pathway, as a myriad of different motor control problems (e.g. co-contraction, associated reactions) that together may fall under the umbrella term of "spasticity".

Thus, the challenge for clinicians is to establish the most appropriate time, content and intensity of rehabilitation for individuals following a brain lesion, in order to enhance the functionality of ensuing neuroplastic changes. Additionally, these changes should be designed to be long-term. At a behavioural level then, how may the skill acquisition process be structured to drive these changes most effectively? Section 1.6 will address this important question.

Table 1.6
Processes mediating neuroplasticity
Examples of neuroplastic changes at different levels of analysis

Level of analysis	Change	Reference
Molecular	Changes in amounts of individual neurotransmitters (e.g. glutamate)	Ergenzinger and Pons (2000)
	Change in balance between different neurotransmitters	Kolb and Whishaw (2000)
	Changes in neurotrophic factors	Kolb and Whishaw (2000) Schallert *et al.*, (2000)
Cellular	Long-term potentiation (LTP) or depression (LTD): changes in synaptic strength	Nudo *et al.*, (2000) Celnik and Cohen (2005) Woldag andHummelsheim (2002)
	Neurogenesis: activation of stem cells	Kolb and Whishaw (2000)
	Collateral sprouting: formation of new connections	Ergenzinger and Pons (2000) Kolb and Whishaw (2000) Lee and van Donkelaar (1995) Celnik and Cohen (2005)
	Unmasking of latent synapses	Ergenzinger and Pons (2000) Lee and van Donkelaar (1995)
	Denervation supersensitivity	Kolb and Whishaw, 1996
	Increased involvement of astrocytes (especially glia)	Ergenzinger and Pons (2000)
	Multiplexing: multiple use of neurons which enables them to participate in different functions	Bach-y-Rita (2000)
Organ	Changes in neurotransmission, either synaptically or through nonsynaptic diffusion neurotransmission (NDN)	Bach-y-Rita (2000)
	Changes in neural network, e.g. through recruitment of: - adjacent undamaged areas, e.g. motor association cortices in affected hemisphere - unmasking functionally dormant pathways - ipsilateral pathways - less-affected hemisphere	Dettmers *et al.*, (in Ploughman,2002) Nelles *et al.*, (1999[a, b]) Lee and van Donkelaar (1995) Turton *et al.*, (1996) Nudo *et al.*,, (1996) Nelles *et al.*, (2001)
	Activation of latent bilateral representation	Wasserman *et al.*(2000)
	Development of novel ipsilateral tract	Carr (2000)

1.5.3. INTENSITY OF TRAINING

As mentioned earlier, several reviews have indicated an association between more intensive therapy and better outcomes after stroke (e.g. Langhorne *et al.,* 1996; Duncan, 1997; Kwakkel *et al.,* 1997[a,b], 1999; Pomeroy and Tallis, 2002; Platz, 2003; van Peppen *et al.,* 2004). Reviewing evidence from physiotherapy as well as occupational therapy interventions, Kwakkel *et al.* (2004) found a small but significant improvement in ADL following augmented exercise, notably in those studies where at least 16 hours of extra therapy time had been provided within the first six months after stroke. In terms of clinical relevance, this was translated into an improvement of approximately 5% (i.e. 1 point on the Barthel Index). This impact could be seen to be negligible, but one needs to consider the lack of sensitivity of the tool whereby it was assessed in most cases, i.e. the Barthel Index. With regards to the question of the optimum intensity of therapy, Kwakkel *et al.* (2004) referred to the variation in augmented treatment time in the literature, which ranged from 132 to 6816 minutes. Apart from the minimum amount of hours reported above, it was not possible to recommend an optimum - although Kwakkel *et al.* (2004) stated they had not observed a ceiling effect in their review.

The benefits of treatment intensity are not unequivocal however; Kwakkel *et al.* (2004) reported that 14 of the 20 RCTs found positive effects associated with more intensive therapy, but six did not. Interestingly, only three studies evaluated the effects of augmented exercise in people in the chronic stage after stroke (i.e. more than six months after the acute event), but none of these focused on the upper limb. Three studies, carried out at an earlier stage that did evaluate upper limb function, yielded no significant benefit of intensive therapy – a finding also reported by Barreca *et al.* (2003).

On balance, given that the review by van Peppen *et al.* (2004) was systematic, more comprehensive and recent than that by Barreca *et al.* (2003), it can be concluded that treatment *intensity* is an important factor in determining outcomes. However, Page (2003) questioned its weight in comparison to the actual *content* of the intervention. He argued that studies failing to show functional benefits were generally based on approaches that did not concentrate on specific skills. Those

that did, often achieved functional goals through programmes that were not necessarily intensive, when compared to standard CIT (which is probably the most intensive form of UL therapy). Weighing up the relative importance of treatment intensity versus task-specificity, Page (2003) argued that the latter was probably a more powerful variable in driving neuroplastic changes mediating functional recovery than the former.

In addition to the nature of tasks being practised and the amount of time spent, it is also important to consider the *organisation* of practice. The evidence from the literature on skill acquisition in non-impaired populations (discussed in more detail in section 1.6) indicates that different practice schedules are likely to have differential effects on immediate and long term retention (e.g. Shea and Morgan, 1979) and that outcomes depend on the task (Lee and Genovese, 1988) as well as on the stage in the learning process (e.g. Shea, Kohl and Indermill 1990). Given that the aim of rehabilitation is to enhance long term retention, it is important that practice be scheduled appropriately (Fuhrer and Keith, 1998). However, most studies fail to specify how practice is scheduled, which needs to be addressed in future research.

1.5.4 SKILL ACQUISITION AFTER STROKE: DOES CURRENT PRACTICE MAKE PERFECT?

On the basis of the available evidence, it is not possible to answer this important question. The sections above showed evidence that many stroke patients continue to be able to improve on tasks involving their affected upper limb, even in the chronic stage. Evidence cited in the previous sections also indicated *what* should be practised, i.e. functionally relevant skills instead of mere movement. But is the process of practice optimally designed to achieve long-term carry-over into meaningful, every-day activity? Fuhrer and Keith (1998) were of the opinion that most therapists structure the practice process on the basis of intuition rather than evidence, despite a considerable body of literature on skill acquisition in the non-impaired population indicating that intuitive methods may not be optimal to enhance long term retention. Numerous authors have emphasised the importance and the potential of this body of literature for neurological rehabilitation (e.g. Marteniuk, 1979; Lee *et al.*, 1991; Poole, 1991; Winstein, 1991[a,b]; Majsak, 1996; Hochstenbach

and Mulder, 1999; Wishart *et al.*, 2000; Marley *et al.*, 2000; Ezekiel *et al.*, 2000; Lehto, 2000; Shumway-Cook and Woollacott, 1995, 2001), but only very few studies have actually involved people with a CNS lesion in skill acquisition research.

Hanlon (1996) reported the first group study involving 24 chronic stroke patients, comparing different skill acquisition processes involving a functional upper limb task, i.e. blocked practice[8] versus random practice. The results were in favour of the group using the random practice schedule, with performance being superior at retention tests at two and seven days after training. Interestingly, random practice did not seem to affect the rate of acquisition, although participants in this group did complain that they found it difficult to perform the criterion task correctly. This study supports findings from research with non-impaired subjects (pioneered by Shea and Morgan, 1979) demonstrating that random practice is more beneficial for long term retention than blocked practice. Several explanations have been put forward for this finding (discussed in section 1.6) with Hanlon's results being in favour of the hypothesis that random practice requires the subject to generate a solution for a given motor problem each time, whereas blocked practice allows the subject to merely recall the solution. Although the findings from Hanlon's study were promising, there were several limitations; the sample size was relatively small and it was not entirely clear how accuracy of performance – an important outcome measure - had been evaluated. Additionally, there was a potentially confounding variable in that the random practice group included an additional three tasks, which were not part of the blocked practice group and hence the extra practice may have biased the results.

Although this innovative study warranted further work with stroke patients, only Dick *et al.* (2000) seem to have carried out a similar study with patients with Alzheimers Disease. In contrast to Hanlon, they found that random practice was not beneficial and that only constant practice, using the same tasks, facilitated immediate transfer. These findings emphasise that caution should be exercised in generalising findings

[8] Blocked practice is defined as: "*a practice sequence in which individuals repeatedly rehearse the same task.*" (Schmidt and Wrisberg 2000: p. 233). Random practice is defined as "*a practice sequence in which individuals perform a number of different tasks in no particular order, thus avoiding or minimizing consecutive repetitions of any single task.*" (Schmidt and Wrisberg 2000: p. 233).

from motor learning research - which predominantly involved cognitively intact people - to neurological populations.

Taken together, in order to enhance the long-term functional effects of neurological rehabilitation, the efficacy of different skill acquisition processes for patients with a CNS deficit requires further research (Fuhrer and Keith, 1998).

1.5.5 REHABILITATION FOR IMPROVING UPPER LIMB ACTIVITY AFTER STROKE: METHODOLOGICAL ISSUES

Research into the efficacy of physiotherapy after stroke has been hampered by a number of methodological problems, i.e. small and heterogeneous study populations, a lack of information regarding the content of therapeutic interventions and a myriad of outcome measures (Kwakkel *et al.,* 1999[a]; Pollock *et al.,* 2003). As a result, neurological physiotherapy has been labelled as the "black box of therapy" (Ballinger *et al.,* 1999; Pomeroy and Tallis 2002[b]; DeJong *et al.,* 2004). Given these problems, it is not surprising that input - output relationships in this domain have generally been inconclusive.

The issue of inadequate sample size threatens statistical power in a considerable part of the literature, but is difficult to resolve in cases where novel treatments or assessment techniques are explored. Normally, these require to be tested in single-centre studies before they are suitable for multi-centre studies.

The need for therapeutic input to be described more clearly and in more detail has already been emphasised (Partridge and De Weerdt, 1995; Partridge, 2002; Pomeroy and Tallis, 2002[a], DeJong *et al.*, 2004). Additionally, several authors have indicated that it is time to move away from "approaches" or "schools" in neurological physiotherapy and towards the evaluation of specific and clearly described interventions (Platz *et al.,* 1999; Woldag and Hummelsheim, 2002; Pollock et al., 2003; Baer and van Wijck, 2005).

Outcome measurement continues to be a challenge in neurological rehabilitation. A survey charting the use of assessment tools in this domain revealed that outcome assessment was not carried out routinely and lacked standardisation (van Wijck *et al.,* 2001). The most frequently used tools were: the Modified Ashworth Scale (Bohannon and Smith, 1987), the Functional Independence Measure (Granger *et al.,* 1986) and the Fugl-Meyer (Fugl-Meyer *et al.,* 1975), while the ARAT emerged as the most commonly used upper limb function test. The application of measurement technology was minimal, with video and goniometry being used most frequently. Despite the weaknesses of this survey (i.e. a very limited response, biased towards English-speaking countries), the findings indicated that outcome assessment in neurological rehabilitation relies primarily on ordinal level scales. Unfortunately, some of these are known to be poorly standardised (e.g. the ARAT: Patel, 2003; Platz *et al.,* 2005), have questionable validity and reliability (e.g. the Modified Ashworth score: Pandyan *et al.,* 1999), suffer from floor effects (e.g. Box and Blocks test: Platz *et al.,* 2005[c]), ceiling effects, or a lack of specificity and sensitivity (e.g. the Barthel Index: Bakheit *et al.,* 2001, Lai *et al.,* 2002). As a result, it is not inconceivable that specific, clinically relevant but perhaps relatively small changes may have slipped through the maze of outcome assessment in many intervention studies, thus contributing to a Type II error. The same survey also indicated that the main barriers to a more routine use of assessment tools – and in particular measurement technology - were a lack of resources, information and training. In order to improve the evidence base in neurological rehabilitation, it is necessary to address these barriers, primarily by allocating sufficient resources and providing further education to clinicians.

In conclusion, the main recommendations for strengthening the methodology of future clinical trials include: ensuring adequate power, describing therapeutic input clearly and in detail to enable replication, assessing outcomes using valid, reliable and clinically relevant measurement tools, where relevant integrated with measurement technology.

1.5.6 CONCLUSION

Evidence from the general stroke rehabilitation literature was in favour of intensive, task-specific rehabilitation for improving function, but the evidence pertaining to the upper limb was rather more patchy and inconsistent. The literature appeared to be dominated by studies with people in the acute or sub-acute stage after stroke (see Hiraoka, 2001; van der Lee, 2001[b]; Woldag and Hummelsheim, 2002; Platz, 2003 for reviews). The outcomes from some of the strategies targeting the upper limb was equivocal, which could be partially explained by the lack of detail in the description of the therapeutic input and the variation in the intensity between studies and partially by other methodological problems, highlighted in section 1.5.5.

Given the prevalence, severity and impact of upper limb activity limitations after stroke (section 1.1), together with the tentative evidence that improvements may still be achievable through rehabilitation in the chronic stage, further research into the effects of task-specific practice on UL function is warranted. A particular challenge is the design of effective rehabilitation for people with spasticity. As discussed in section 1.3, one way to target focal spasticity is through botulinum toxin type-A, which reduces the peripheral expression of spasticity (i.e. at the level of the neuromuscular junction). However, BTX-A does not alter the *central* problems involved in coordination, which may affect the execution of functional skills. Thus, rehabilitation for people with limited arm function and spasticity after stroke should foster neuroplastic changes in the CNS that enable and sustain goal-orientated activity in the long term. This section of the literature review provided converging evidence from clinical and neurophysiological studies that this could be mediated through intensive practice of functionally meaningful tasks. However, this assumption would need to be formally tested, since section 1.4 showed an absence of published studies investigating the differential effects of exercise or task-specific training, when provided together with BTX-A.

A further question emerging from this review that needs to be addressed is how task-specific practice should be structured in order to achieve long-term carry-over into meaningful activity. This issue will be explored in the following section.

1.6 ENHANCING SKILL ACQUISITION IN NON-IMPAIRED POPULATIONS

1.6.1 INTRODUCTION

The previous section of this chapter highlighted that there was, at the time of writing, a dearth of literature on the effects of different learning strategies in neurological rehabilitation. In contrast, the motor learning literature featuring non-impaired people is considerable. This research domain was developed primarily within the context of experimental psychology and physical education, with pioneers such as Adams (1971) and Schmidt (1975, 1988). A review of this body of literature is beyond the scope of this thesis and the reader is referred to textbooks instead (e.g. Magill 2001, Schmidt and Lee 1999, Schmidt and Wrisberg 2000). The section below is merely a brief summary - which inevitably fails to do justice to the abundance and sophistication of much of the research undertaken in this area – of the key principles of skill acquisition that may be directly relevant to stroke rehabilitation. The purpose of this section is to inform the structure of the feasibility study, featuring task-specific practice, in Chapters Three to Five.

Detailing the process of motor learning, Fitts and Posner (1967, cited in Magill, 2001), proposed that skill acquisition goes through three stages, ordered along a continuum: the cognitive, associative and the autonomous stage. Typical characteristics of each of these stages are listed in table 1.7.

Table 1.7
The three stages of learning and their characteristics
According to Fitts and Posner (1967), cited in Magill (2001).

Stage	Characteristics
Cognitive	▪ The learner is concerned with "getting the idea" of the task ▪ Cognitive processes are required to identify the goal of the task and generate a solution re. how to achieve it ▪ Performance varies between attempts and is characterised by large and frequent errors
Associative	▪ The learner becomes increasingly proficient in associating aspects of the environment with the actions required to achieve the goal ▪ Performance is being refined, errors become smaller and less frequent
Autonomous	▪ The learner is fully proficient, able to adjust the skill to changing demands and correct errors ▪ Performance is automatic and consistent

It is only after extensive practice that the learner may reach the autonomous stage, where performance is automatic and cognitive effort is minimal (Magill, 2001). This, ideally, would be the final stage of rehabilitation, but anyone, especially people with brain damage, many remain at some point in the associative stage. A challenge for clinicians is to facilitate the learning process in such a way that patients progress along the continuum as safely, efficiently and as far as possible.

It is important to make the distinction between performance and learning. Performance is subject to temporary influences (e.g. fatigue, pain, motivation or just luck) and therefore a satisfactory performance does not automatically represent long-term retention. In contrast, learning has been defined as:

> "*a change in the capability of a person to perform a skill. It must be inferred from a relatively permanent improvement in performance as a result of practice or experience*" (Magill, 2001: p. 352).

Learning needs to be assessed on a retention test, i.e. after an appropriate delay during which no practice is undertaken and which allows any performance effects to dissipate (Magill, 2001), as this demonstrates to what extent the memory is long-term. Additionally, learning needs to be assessed on a transfer test, which is a slight variation from the task that has been practised. This will reveal to what extent the learner is able to adapt what has been learned.

In rehabilitation, clinicians may be inclined to schedule practice in such a way that it enhances performance during a treatment session, the obvious benefit being that it boosts motivation in both patient and therapist. A potential drawback, however, is that strategies that enhance performance in the clinic may not necessarily enhance learning or transfer into ADL. In fact, Taub and Wolf (1997, cited by Bach-y-Rita 2000: p. 368) highlighted that the limited transfer of treatment into real life or even into the next session, which is common in neurological rehabilitation, is often misinterpreted as a plateau in the person's ability to progress, which unfortunately may lead to the decision to discontinue rehabilitation. Therefore, it is important that clinicians aim to facilitate learning, rather than boost mere performance (Wishart *et al.,* 2001; Lehto *et al.,* 2001).

Three important factors that can be modified by the therapist and which have an important influence on the learning process are goal setting, practice and augmented feedback (Schmidt and Lee, 1999; Magill, 2001; Schmidt and Wrisberg, 2000). The next sections will highlight the importance of goal setting and present characteristics of practice and feedback schedules that have been shown to promote learning. Although the boundaries between the successive stages of skill acquisition are not clear-cut, an understanding of their characteristics is important nevertheless, since the needs of the learner depend on the stage they are in.

1.6.2 GOAL SETTING

Crucial to achieving success in any learning process is the motivation of the learner, which may be enhanced through the process of goal setting, whether in an educational setting (Schmidt and Lee, Wrisberg, 2000) or in rehabilitation (Wade 1999[a,d]). The technique of goal setting has been studied extensively in general psychology. Research has shown that goals should be specific, measurable, achievable, relevant and time-limited (Smith, 1993; Barnes and Ward, 2000; Wade, 1999[b]). Although goal setting in clinical practice is normally undertaken by clinicians, an important question is how they ensure that their goals are relevant for the patient. Since the goals set by patients may be different from those set by health care practitioners (Reid and Chesson, 1998; Wade, 1999[c]), patients need to be involved in the goal setting process.

1.6.3 ORGANISING PRACTICE

Variables related to the organisation of practice, which will be discussed below, are: the amount, distribution, type of practice and practice variation. Key terms are defined in table 1.8.

Amount

The amount of practice required to learn a skill has been much debated in the motor learning literature, which resonates in the stroke literature under the heading of "intensity" (see section 1.5.3). Although there are no set rules for the number of attempts that are required, the motor learning literature generally agrees on the principle of "overlearning", i.e. of continuing practice beyond the point of a certain performance criterion (Magill, 2001). Unfortunately however, due to resource constraints, it is doubtful whether this will ever be achieved in a publicly funded health care setting. Nevertheless, clinicians need to provide opportunities for practice wherever feasible.

Distribution

Related to the absolute amount of practice is the distribution of practice within a treatment session. A "massed" schedule involves more practice than rest, whereas in a "distributed" session, the opposite is the case. Following much debate in the literature, a comprehensive review by Lee and Genovese (1988) indicated that distributed practice tends to be more effective than massed practice for continuous skills, whereas the opposite applies to discrete skills. However, in the context of stroke rehabilitation, frequent rests may be necessary in any case in order to avoid fatigue because of the associated health and safety hazards.

Table 1.8
Glossary of terms related to skill acquisition

TERM	DEFINITION
Type of skill	
Discrete	A task with a clearly defined start and end (e.g. pointing)
Serial	A task consisting of a sequence of several discrete tasks (e.g. dressing)
Continuous	An ongoing, often cyclical, task, with no clearly defined start and end (e.g. driving)
Practice	
Physical	A form of practice involving observable behaviour
Mental	"The cognitive rehearsal of a physical skill in the absence of overt physical movements. It usually involves imaging oneself performing a skill." (Magill, 2001: p. 352)
Blocked	"A practice sequence in which individuals repeatedly rehearse the same task." (Schmidt and Wrisberg 2000: p. 233)
Random	"A practice sequence in which individuals perform a number of different tasks in no particular order, thus avoiding or minimizing consecutive repetitions of any single task." (Schmidt and Wrisberg 2000: p. 233)
Constant	"A practice sequence in which individuals rehearse only one variation of a given class of tasks during a session." (Schmidt and Wrisberg 2000: p. 243)
Varied	"A practice sequence in which individuals rehearse a number of variations of a given class of tasks during a session; also referred to as variable practice." (Schmidt and Wrisberg 2000: p. 244)
Whole	A form of practice involving the rehearsal of a task in its entirety.
Part	A form of practice involving the rehearsal of components of a task.
Augmented Feedback	"A generic term used to describe information about performing a skill that is added to sensory feedback and comes from a source external to the person performing the skill." (Magill, 2001: p.349)
KR (knowledge of results)	" Augmented, usually verbalizable information provided after the action is completed that indicates something about the degree to which the performer achieved the desired movement outcome or environmental goal." (Schmidt and Wrisberg 2000: p. 258)
KP (knowledge of performance)	"Augmented feedback that provides information about the quality of the movement a performer has produced; sometimes referred to as kinematic feedback." (Schmidt and Wrisberg 2000: p. 260)
Faded	"A schedule for providing extrinsic feedback in which relative frequency of feedback is high during initial performance attempts and diminished during later learning. "(Schmidt and Wrisberg 2000: p. 279)
Relative feedback frequency	"The proportion of performance attempts for which feedback is given; equal to absolute feedback frequency divided by the number of performance attempts and multiplied by 100." (Schmidt and Wrisberg 2000: p. 279)
Absolute feedback frequency	"The total number of feedback presentations given for a series of performance attempts." (Schmidt and Wrisberg 2000: p. 278)

Type of practice

Practice may be overt (i.e. observable action) or covert (e.g. intending, imagining or observing an action). According to Jeannerod (2005), overt and covert action may be placed along a continuum:

> *"Covert and overt stages represent a continuum, such that every overtly executed action implies the existence of a covert stage, whereas a covert action does not necessarily become an overt action"* (Jeannerod, 2005: p. 173).

The rationale for placing overt and covert activity along a continuum is that there is evidence to suggest that these forms of action share the same representations, both in behavioural and in neuronal terms (Jeannerod, 2005). Jeannerod's interpretation also suggests that covert action may help to prepare the actual overt behaviour.

In applied settings such as physical education and rehabilitation, observation of a skill performed by a third person is common practice, but Magill (2001) pointed out that this process has not been well researched. Demonstration is associated (and often used interchangeably) with observational learning, which has been investigated extensively, notably in the pioneering work of Bandura (1984). What is actually being learned from a demonstration? Research has suggested that human perception of movement is not concerned with the kinematics of individual limb segments *per se*, but rather with the relative relationships between them, which reveal the invariant characteristics of a particular movement pattern (Magill, 2001). Magill and Schoenfelder-Zohdi (1996) showed that demonstration tends to be effective when learners acquire a novel pattern of coordination, but not when they merely extend their repertoire of parameters (e.g. absolute duration or force) for patterns of movement they already master. Thus, in stroke rehabilitation, demonstration may be important in cases where the aim for the patient is to alter compensatory patterns or unwanted synergies and learn new movement patterns.

What is the neuronal correlate of observational learning? The discovery of the so-called "mirror neuron system" may provide an interesting insight into this phenomenon. Mirror neurons, first discovered in the premotor cortex of monkeys by Di Pellegrini in 1992 (Rizzolatti and Fadiga, 2005) are neurons that discharge when presented with stimuli that represent activities in which an experimenter or the monkey itself interact with an object. Several studies using a variety of neuro-imaging techniques have since established the equivalent system in humans (for an

overview see Rizzolatti and Fadiga, 2005). The results from this work have led to the development of the "direct matching hypothesis" (Rizzolatti and Fadiga, 2005), which postulates that by observing an actor interacting with an object, the visual representation of that activity is mapped onto the motor representation of the same activity. In other words, the mirror neuron system matches action-observation with action- execution[1]. When these two representations "resonate", it is thought that the action is being understood[2]. In summary, based on these studies, demonstration enables the learner to prepare for an action by eliciting specific activity in the mirror neuron system.

Another form of covert action, i.e. mental practice, was introduced in section 1.5.2.8. Mental practice is commonly used in sports, dance and martial arts (e.g. for a review see Feltz and Landers, 1983). It is based on the so-called "ideomotor theory", which dates back to the German philosopher Lotze and William James in the late 19th century (Knoblich and Prinz, 2005). As Knoblich and Prinz (2005: p. 81) explained, the assumption underpinning this theory is that:

> *"an intention to achieve certain perceivable consequences is sufficient to fully specify certain motor commands".*

As such, imagining an action is thought to play a role in inverse modelling of motor control, i.e. where specific environmental outcomes determine the required motor programme.

An important question refers to the most effective type of practice or, in cases where they are combined, the most effective mix of different types of practice. This question was addressed in an interesting study by Hird *et al.* (1991). The results showed that physical practice (PP) was superior to mental practice (MP), which in turn was superior to no practice at all. When combining PP and MP, a higher proportion of PP was more effective than a smaller proportion. However, on one of

[1] Interestingly, visual stimuli pertaining to the object *per se* or a simulated activity do not trigger a response in the mirror neuron system (Rizzolatti and Fadiga 2005), which suggests that only occupational embedded observation (i.e. the "real thing") would be effective in activating mirror neurons.

[2] The reason why observational learning may not necessarily result in overt activity, according to Rizzolatti and Luppino (2001, cited in Rizzolatti and Fadiga 2005), is that modulation at the spinal level may be counterbalanced by cortical output, as shown in a study by Baldissera *et al.* (2001) using the H-reflex to investigate the modulation of spinal cord excitability.

the two tasks in the experiment, an equal combination of PP and MP was as effective as PP alone. These findings suggest that PP should be undertaken wherever possible, but that MP may supplement learning effectively where PP is not possible.

In an interesting study, Kohl et al. (1992) compared the effects of five different training schedules (i.e. a PP only, MP only, alternating MP with PP, alternating PP with rest and no training), on performance of a pursuit rotor task in a group of non-impaired young adults. The number of practice trials was equal for the first four groups. The results indicated that the accuracy scores for the two groups using PP only and alternating MP with PP were not significantly different from each other but were significantly greater than the other three groups, when retention testing involved the ipsilateral arm. Interestingly, when they used the same protocol in a second experiment, but involved the contralateral arm in the retention test, the alternating MP with PP condition yielded significantly greater scores than all other groups, including the PP only group. This indicates that alternating MP with PP may be superior to PP in terms of transfer to a related but not identical activity and thus be superior in terms of actual learning. Taken together, these results suggest that MP may not only act as a substitute for a proportion of PP trials, but may actually facilitate learning more than when only PP is used. This is an interesting idea for clinical applications, where fatigue may limit the amount of PP a patient is able to undertake and where therapist time may be limited.

In a further study, Hanaghan (2003) investigated whether there would be any difference in terms of speed and accuracy in performing a novel lower limb precision task between two groups, one of which practiced using PP *en bloc*, followed by MP *en bloc* and one of which alternated MP and PP. The results showed superior learning effects in terms of accuracy in the second group, whereas both groups improved to a similar extent in terms of speed. These results suggest that it may be more beneficial to intersperse PP with MP than to cluster PP and MP in blocks of practice.

How may the effects of MP be explained? At present, the two most commonly accepted theories explaining the effects of mental practice are the psychoneuromuscular theory and the central representation theory (Mulder *et al.*, 2004). Very briefly, the former postulates that mental practice involves the same

neuromuscular pathways as physical practice of the same task, while the latter suggests that the same motor programming processes are involved. Taken together, these theories suggest that, both at the "hardware" (i.e. neuronal-musculoskeletal) and at the "software" (i.e. behavioural) level, mental and physical practice involve similar processes – with the exception of actual motor output, which is withheld during mental practice.

The neurophysiological basis of mental practice has been reviewed by several authors (e.g. Decety, 1996; Kosslyn *et al.,* 2001). A number of studies with non-brain damaged subjects have indicated partial overlap between the neural networks involved in mental and actual movement (e.g. Porro *et al.,* 1996, Gerardin *et al.,* 2000). Several studies have shown that mental practice increases cortical excitability, resulting in enhanced magnetic motor evoked potentials (Kiers *et al.,* 1997; Hashimoto and Rothwell, 1999; Fadiga *et al.,* 1999), even in the absence of EMG output. These findings are particularly interesting for stroke rehabilitation, as Traversa *et al.* (1997) showed that the excitability threshold for motor evoked potentials in the affected hemisphere was significantly higher compared to the unaffected hemisphere and non-impaired controls and that clinical recovery was associated with increased excitability of the motor output area.

Taken together, MP appears to be an effective additional strategy for learning novel tasks. Physical practice is required to obtain the necessary experience, but substituting a proportion of PP with MP may actually yield superior effects than through using PP alone. This may be explained by MP and PP of the same task sharing similar representations, with MP priming the processes and neural networks that are required for the subsequent action.

Practice variation

In order to apply functional skills, practised in a rehabilitation setting, to an actual ADL situation, the learner needs to be able to adapt to different task and environmental requirements. How may practice be structured to enhance transfer between these two settings? Practice may either involve sheer repetition of the same task (i.e. "drill") or be varied through different variations of the same category of tasks, different categories of tasks, or both.

Constant practice implies that the same variation of a task is repeated, whereas variable practice includes different variations of the same category of task (table 5.3). When practice includes different categories of tasks altogether, the order of tasks may be blocked (i.e. the same task is repeated over and over again), or random (i.e. different tasks are practised in random order). In contrast to popular belief, several studies have shown that although blocked practice may enhance performance, it is actually detrimental to learning, when compared to random practice (Schmidt and Lee, 1999). The first study to demonstrate this surprising finding was published by Shea and Morgan (1979), which has generated considerable research on this topic since (e.g. see Brady, 1998, for a review). The positive effect of random practice is known as the "contextual interference effect" (Magill, 2001). With numerous factors influencing the skill acquisition process (e.g. level, age and condition of the learner, the type of skill, the environment in which it is undertaken), it is not possible to stipulate an optimal level of contextual interference. However, the overall picture emerging from research on this topic is that although high contextual interference (as in random practice) may impair performance, it is more likely to enhance retention and transfer than low contextual interference (as in blocked practice).

Two main theories have been put forward to explain these findings: the elaboration hypothesis (Shea and Zimny, 1983) and the action plan reconstruction (or forgetting) hypothesis (Lee and Magill, 1985). The former predicts that contextual interference produces better learning, as the learner elaborates on their experiences by comparing and contrasting different tasks, which produces more meaningful and distinctive memories and thereby enhances long-term retention. In contrast, the latter theory suggests that contextual interference makes learners forget how they solved a particular motor problem, which requires them to reconstruct their action plan each time they attempt a task. This is in contrast to blocked practice, which allows the learner to merely recall the solution. There is evidence to support both hypotheses (Magill, 2001). In fact, they could both be accommodated by a neural network perspective, since common to both hypotheses is the notion that random practice involves more intensive, task-specific information processing compared to blocked practice. This might well explain, in a Hebbian manner (Kandel *et al.*, 2000), how random practice may enhance long-term retention, as it activates

specific neural networks, associated with a particular function, every time the task is being undertaken.

With regards to constant and variable practice, a considerable body of research (e.g. see Magill, 2001) indicates that variable practice tends to produce better retention and transfer than constant practice. Only in the initial stage of learning does constant practice yield better results than varied practice (Schmidt and Wrisberg, 2000), as the learner is forming "the idea" of the task. These findings may be explained on the basis of Schmidt's schema theory (see Schmidt, 1988; Schmidt and Lee, 1999 for a full account), which postulates that learners develop a generalised motor programme for each specific class of activities. Exposure to a wide range of variations of the same task would enable the learner to input a range of different parameters (i.e. absolute force, absolute time and specific effectors required) into the programme, which would strengthen the generalised motor programme in terms of its ability to transfer to different task and environmental demands (whilst staying within the boundaries of the generalised motor programme). In contrast, constant practice would only develop part of the generalised motor programme, which would therefore be inadequate if task was required to be adapted.

In summary, with regards to structuring the learning process as a whole, blocked practice is thought to be most effective in the cognitive stage of learning, as it enables the learner to establish a consistent image of the act (Shea, Kohl and Indermill, 1990). For the same reason, constant practice is also more effective at this stage than variable practice. However, as soon as the learner has passed this stage, evidence suggests that practice needs to be varied, through variable and/ or random practice (Marley *et al.,* 2001; Poole 1991) in order to strengthen the generalised motor programme and to enhance its long term retention (Schmidt and Wrisberg, 2000).

1.6.4 ORGANISING AUGMENTED FEEDBACK

Augmented feedback (hereafter abbreviated to "feedback"), i.e. feedback provided by an extrinsic source, may exert a powerful influence on the learning process. The following section will address the different types, the amount and the timing of feedback.

Types of feedback

In clinical practice, different types of feedback are used, including auditory, visual, tactile and proprioceptive modalities. Feedback may be primarily motivational in nature and provide general encouragement and positive reinforcement, with the aim to increase the probability that the behaviour will be repeated in future (according to Thorndike's (1927) Law of Effect, cited in Bernstein, 2006). Feedback may also provide specific information about the performance; about the outcome (so-called "knowledge of results", or KR) or the movement pattern (so-called "knowledge of performance", or KP). Research supports the notion that both motivational and information feedback are important and also that both KP and KR are valuable. However, there is no clear-cut evidence to suggest which type is superior, as this depends on the characteristics of the learner, as well as the task to be learned (Magill, 2001).

Amount

The traditional (and still commonly held) belief is that more feedback is better (Schmidt and Wrisberg, 2000). However, where learners have intact error-detection capabilities and where there is a clear environmental criterion that the learner can perceive, augmented feedback may be redundant (Magill, 2001). Furthermore, several studies have shown that abundant feedback may enhance performance, but actually impair learning, whereas less feedback may enhance learning (e.g. the interesting study by Winstein and Schmidt, 1990). To explain this finding, the "guidance hypothesis" has been put forward, which postulates that frequent augmented feedback may interfere with independent problem solving (Magill, 2001). Thus, when required to perform without it, those who have been provided with feedback all along may perform worse than those who have been given intermittent feedback only. Again, there is no hard and fast rule regarding the optimal frequency

of feedback, as this appears to depend on the complexity of the skill (Magill, 2001). In relation to the stages of learning, it has been shown that frequent feedback enhances learning in the cognitive stage, as it enables the development of an accurate image of the act. However, as soon as this stage is passed, the learner should be given an opportunity to evaluate his/ her performance independently.

The literature suggests different strategies for rationing feedback, including summary feedback, average feedback, bandwidth and fading feedback (Magill, 2001; Schmidt and Wrisberg, 2000). Summary feedback involves providing a summary on a number of attempts only, with the number of attempts depending on task complexity (Schmidt and Wrisberg, 2000). For average feedback, information is averaged over several attempts. (For clinical practice, the distinction between these two variations is probably not relevant.) Bandwidth feedback refers to the margin of error that is allowed; only if performance falls outwith a certain margin will the learner be given feedback. Sherwood (1988) was the first to show that bandwidth feedback is more effective than feedback after every trial, whilst others have demonstrated that there is no significant benefit to be had from changing the bandwidth as learning progresses (e.g. Goodwin and Meeuwsen, 1995; Lai and Shea, 1999). In order to increase the opportunity for independent problem-solving, faded feedback may be implemented, which involves a relatively high frequency of feedback in the cognitive stage of learning, which gradually diminishes as learning progresses (Schmidt and Wrisberg, 2000).

Timing

Feedback may be delivered concurrently or terminally (and either with or without a delay). Concurrent feedback appears to be useful in situations where intrinsic feedback is lacking (Magill, 2001) and although this would appear to be useful for patients with sensory impairments due to brain damage, there is concern for information overload. Therefore, this form of feedback will not be further considered here.

An interesting study by Swinnen *et al.,* (1990) showed that providing instantaneous terminal feedback was detrimental to retention when compared to delaying the feedback for a few seconds. It was postulated that the delay enables learners to engage in independent error-detection, which would enhance their problem-solving

abilities (Magill, 2001). However, the literature provides no conclusive evidence on the optimum post KR or post KP interval (Magill, 2001).

In summary, research evidence suggests that in the cognitive stage of learning, frequent augmented feedback is most effective, not only to motivate the learner, but also to provide relevant information on how to improve performance. However, dependency should be avoided and learners should be given sufficient opportunity to engage in independent problem solving. Therefore, as the learner progresses, feedback should be gradually withdrawn (Ezekiel *et al.,* 2001).

Manual Guidance

Perhaps one of the most characteristic components of physiotherapy practice - applied with great skill and dedication – is manual guidance. But what is the evidence to support its effectiveness? In an eye-opening study, Annett (1959, cited in Schmidt and Wrisberg, 2000) showed that although manual guidance improved performance, it was detrimental on a retention test where manual guidance was not available. This finding can be explained on the basis of Schmidt's generalised motor programme theory (Schmidt, 1988): manual guidance alters the input to the system and changes the sensation and perception of the task. In terms of selecting the correct generalised motor programme, decisions are already made by the therapist in such a way that any errors are minimised. Although performance may appear to be satisfactory, the question is whether it can be transferred to a situation where guidance is not available. It is not surprising that performance is impaired, when a learner is required to perform a task that was practised with manual guidance independently, since the encoding process (i.e. with manual guidance) does not match the retrieval process (i.e. without guidance). Thus, manual guidance acts as a feed-forward, as well as an on-line feedback mechanism, which deprives the learner of independent planning and problem solving.

In summary, in the cognitive stage, manual guidance may be effective, as it conveys to the learner how to solve the problem of performing the task (Schmidt and Lee, 1999). Clearly, in cases where safety is an issue, manual guidance may continue to be required. However, apart from these situations, research indicates that manual guidance should be used sparingly and judiciously (Schmidt and Lee, 1999, Lehto *et al.,* 2001).

1.6.5 SELECTING THE PRACTICE ENVIRONMENT

Given the important role of the environment on motor control (Shumway-Cook and Woollacott, 1995) and the specificity of learning principle (Proteau *et al.*,, 1992) the practice environment should, ideally, be identical to the environment where the task is to be carried out. However, given resource constraints and health and safety issues in clinical practice, it is often not practicable to treat patients in their own environment.

With respect to the tasks themselves, a number of authors have reported benefits from occupational embedding of tasks. For example, Trombly and Wu (1999) showed that stroke patients engaging in goal-directed movements involving real-life objects showed considerably better performance than when they simulated the activity. Similar findings have been confirmed in other studies with stroke patients (e.g. van Vliet *et al.,* 1995; Nelson *et al.,* 1996; Wu *et al.,* 1998[a], Wu *et al.,* 2000 and for a review, see Wu *et al.,* 1998[b]).

1.6.6 SKILL ACQUISITION LITERATURE: SOME CRITICAL NOTES

At this stage, it may be prudent to place some critical notes besides the skill acquisition literature, summarised in the preceding sections. Firstly, Schmidt's generalised motor programme theory is not without problems – as acknowledged by Schmidt himself (Schmidt, 1975). A full discussion of the strengths and limitations of this model is out with the scope of this chapter, but briefly, the main problems refer to the storage question (i.e. is there enough space to store all the programmes?), the novelty question (i.e. how does perfect performance arise without prior practice?) and the inability to explain satisfactorily the phenomenon of transitions in (human) movement, such as those described by Haken et al. (1985). Fundamentally, Schmidt's theory involves a rather uncomfortable philosophical conundrum that involves infinite regression: who compiles the generalised motor programmes?[3] There are a number of alternative motor control models that are not based on a motor program paradigm, e.g. Dynamical Systems Theory (pioneered by Bernstein, 1967), Direct Perception (founded by Gibson (1979) and further developed by Lee (e.g. Lee and Aronson (1974)), some of which avoid a number of

[3] This question refers to the existence of a "homunculus", which is likely to remain elusive...

these pitfalls and provide more robust explanations for research findings which do not easily fit within Schmidt's model. However, a distinct advantage of Schmidt's model is that it is directly applicable to the behavioural level of rehabilitation practice.

Secondly, with regards to the external validity of the general motor learning literature for neurological rehabilitation, it is important to point out that most of the work has been carried out with young, non-impaired adults in the context of physical education. Much of the earlier work took place in laboratory settings with highly constrained (and often rather contrived) perceptuo-motor skills which were sometimes ballistic and often involved only a limited number of degrees of freedom (Leonard, 1998). The step to a neurological rehabilitation setting is considerable in many ways and care must be taken when applying the evidence to stroke rehabilitation. In the clinical context, learners may have multiple cognitive and/ or perceptuo-motor impairments that may affect their learning, activities are often self-paced, involve numerous degrees of freedom and involve a range of different objects, while the environment may be more complex and unpredictable.

Whilst acknowledging these limitations of this body of skill acquisition research, especially its restricted external validity with regards to stroke rehabilitation, it is important to reiterate the comment placed by Fuhrer and Keith (1998), which was that there is a clear need to improve the effectiveness of skill acquisition in neurological rehabilitation. Further research is urgently required, for which this body of literature forms a promising starting point.

1.7 SYNTHESIS: RECOMMENDATIONS FOR A SKILL ACQUISITION PROGRAMME TO ENHANCE FUNCTIONAL UPPER LIMB ACTIVITY FOLLOWING BOTULINUM TOXIN TYPE-A IN STROKE

In summarising this chapter, section 1.1 served to highlight the nature, persistence and severity of UL impairments (in particular spasticity) and functional activity after stroke, which may continue to impact on independence and mood, long after the acute event. There was evidence to suggest that it may still be possible to reduce these problems in the chronic stage after stroke, although this was limited and equivocal.

Section 1.2 focused on the problem of spasticity, clarified the definition of this concept as an umbrella term for all active, positive features of the UMN syndrome and put forward recommendations for the measurement of spasticity. These included the use of technology whereby the biomechanical component could be distinguished from the neurogenic component of RTPM. A novel spasticity measurement device, incorporating these recommendations, will be piloted in Chapter Two.

Section 1.3 continued on the theme of spasticity and systematically reviewed the evidence underpinning BTX-A in the management of focal UL spasticity after stroke. This section highlighted the limited extent of the evidence base, the flaws in the methodology pertaining to the evaluation of the effects on spasticity and the dearth of evidence regarding the impact on UL functional activity as well as participation.

Section 1.4 further explored the evidence on BTX-A and demonstrated that there was little research on the differential effects of additional treatment, when combined with BTX-A. In particular, there was no indication in the literature that the additional effects of task-specific practice, when provided together with BTX-A, had been investigated.

Section 1.5 returned to the issue of arm function after stroke and critically evaluated the efficacy of a range of treatment strategies. Studies involving people in the chronic stage after stroke were outnumbered by those concentrating on the (sub) acute stage, leaving a limited evidence base. Two ingredients emerged from the general stroke rehabilitation literature as important factors in determining the efficacy of the intervention, i.e. task-specific practice and treatment intensity - but evidence pertaining to the upper limb rehabilitation was less robust. However, the clinical literature together with the neurophysiological and behavioural studies discussed in this section provided a converging line of evidence to support intensive training of functionally relevant tasks, incorporating independent problem-solving. However, there was a clear gap in the literature pertaining to the question as to how task-specific practice should be structured in order to achieve long-term carry-over into functional activity.

This issue was addressed in section 1.6, where the literature on motor learning involving non-impaired populations was summarised. The process of skill acquisition has been characterised most eloquently by Nikolai Bernstein, the giant of Russian physiology, whose eminent work continues to inspire:

> *"The process of practice towards the achievement of new motor habits essentially consists in the gradual success of a search for optimal motor solutions to the appropriate problems. Because of this, practice, when properly undertaken, does not consist in repeating the means of a solution of a motor problem time after time, but in the process of solving this problem again and again"* (Bernstein, 1967, cited in Schmidt and Wrisberg 2000: p. 241).

Taken together, this body of literature suggested that both practice and feedback need to be organised in such a way that, in the cognitive stage of learning, a clear image of the act is provided. Upon entering the associative stage, the learner should be given the opportunity - wherever safe - to engage in increasingly independent problem solving, while maintaining high levels of motivation. Given the specificity of learning principle, the rehabilitation process needs to be designed in such a way that it engages the learner in transfer-appropriate processing. In other words, it is important to analyse which cognitive and perceptuo-motor processes will be required for the retrieval of skills (i.e. in actual ADL) and ensure that they are incorporated in the practice process. Additionally, the opportunity for practice needs to be abundant.

An important weakness of this body of literature was its external validity with respect to neurological rehabilitation, since most studies had involved non-impaired populations. The need for research into the effects of different practice and feedback schedules in people with CNS lesions was highlighted.

Thus, each of these strands of the literature review informed the content, organisation and selection of outcome measures for the randomised controlled feasibility study combining BTX-A with an evidence-based functional skill acquisition programme. Before embarking on this study, pilot work was required to test the spasticity measurement device (described in section 1.2 4.2) in terms of its scientific properties and practical feasibility. This study will be reported in Chapter Two.

CHAPTER TWO

MEASURING THE EFFECTS OF BOTULINUM TOXIN ON UPPER LIMB SPASTICITY: A PILOT STUDY

2.1 INTRODUCTION

In section 1.2.6, the recommendation was put forward that a spasticity measurement device should not only measure biomechanical, but also neurophysiological variables. In addition, it should be possible to implement the device in a clinical setting with patients presenting with different levels of spasticity. One of the instruments that incorporated these recommendations was the system developed by Pandyan *et al.* (2001). This chapter presents a pilot study testing the properties of this system.

The aims of this exploratory study were firstly to pilot this device and also to explore the effects of BTX-A on spasticity and RTPM, quantified with this device. Additionally, effects on arm function, as well as participant satisfaction in a cohort study of people with chronic UL spasticity after stroke were investigated. It was considered to be of interest to explore the effects of the treatment both on RTPM and EMG, as well as the velocity-dependency of these variables, since velocity-dependency of the stretch reflex is the hallmark of spasticity, according to Lance (1980). Therefore, RTPM and EMG were assessed during a slow as well as a brisk movement of the affected arm, with the brisk movement resembling the Modified Ashworth manoeuvre (Bohannon and Smith, 1987), as applied in clinical practice. Since it was important to be able to compare the findings from this study with the published literature, the Modified Ashworth Scale was included to obtain a clinical

impression of RTPM, while the Action Research Arm Test was chosen as this is the most frequently reported, validated UL function measure, used in neurological rehabilitation (van Wijck et al., 2001). The following section will concentrate on spasticity, RTPM, arm function and patient satisfaction.

2.2 AIMS AND HYPOTHESES

The primary aim of this pilot study was to:

- Establish the scientific properties and clinical utility of the spasticity measurement device, developed by Pandyan *et al.* (2001)

The secondary aim of this pilot study was to:

- Explore the effects of BTX-A injected into UL muscles including the m. biceps brachii of people with chronic spasticity after stroke, on:
  - Clinically assessed resistance to passive elbow extension, using the Modified Ashworth Scale (MAS)
  - Biomechanically measured resistance to passive elbow extension during the MAS ($RTPM_{fast}$) as well as the velocity-dependency of RTPM, defined as the difference between RTPM during fast passive elbow extension ($RTPM_{fast}$) and slow passive elbow extension ($RTPM_{slow}$), quantified using the device developed by Pandyan *et al.* (2001).
  - Spasticity of the elbow flexors, measured as surface EMG during the MAS (EMG_{fast}), as well as its velocity-dependency, defined as the difference in EMG during fast passive elbow extension (EMG_{fast}) and slow passive elbow extension (EMG_{slow}). This was quantified using a Delsys system (Delsys Inc., USA), which had been interfaced with the device developed by Pandyan *et al.* 2001).
  - UL function, assessed using the Action Research Arm Test (ARAT, Lyle, 1981)
  - Participant satisfaction, indicated on a visual analogue scale (VAS)

These effects were assessed at baseline and four weeks after the BTX-A injection, as this falls within the period where the treatment effects are expected to be most pronounced (Simpson *et al.,* 1996).

The hypotheses tested in this study are listed in Box 2.1. All tests were two-tailed, with alpha set at 0.05.

Box 2.1
Study hypotheses

BTX-A: botulinum toxin type-A. MAS: Modified Ashworth Scale for passive elbow extension. $RTPM_{slow}$: Resistance to slow passive elbow extension, $RTPM_{fast}$: Resistance to fast passive elbow extension, EMG_{slow}: elbow flexor EMG during slow passive elbow extension, EMG_{fast}: elbow flexor EMG during fast passive elbow extension. ARAT: total Action Research Arm Test score.

Aim 1: exploring the effects of BTX-A
H_0A: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference in MAS.
H_0B1: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference in $RTPM_{fast}$
H_0B2: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference in $RTPM_{fast}$ minus $RTPM_{slow}$
H_0C1: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference in EMG_{fast}.
H_0C2: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference in EMG_{fast} minus EMG_{slow}
H_0D: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference in total ARAT score.

2.3 METHODS

2.3.1 DESIGN

This pilot study was designed as a before-after treatment cohort study. Since its aim was primarily of an exploratory nature and because the expected sample size was small, a control group was not included. The study had been approved by the Local Research Ethics Committee.

2.3.2 SAMPLE

Participants were recruited from patients attending the Outpatient Spasticity Clinic of Hunters Moor Regional Neurological Rehabilitation Centre in Newcastle upon Tyne, UK, a regional tertiary rehabilitation centre. Patients were recruited if they met the eligibility criteria listed in Box 2.2 and if, after having been provided with information about the study (Appendix 2.1), they provided informed consent (Appendix 2.2). The presence of contractures was not an exclusion criterion – although those with a

fixed contracture would have been excluded *a priori*, as they would not have been selected for BTX-A treatment in the first place. Those who were given additional pharmacological treatment for spasticity could take part, provided that the treatment had been stable for at least 3 months prior to recruitment and would remain unaltered for the duration of the study.

Box 2.2
Study eligibility criteria
BTX-A: Botulinum toxin type-A, UL: upper limb.

Diagnosis Stroke as confirmed by CT/ MRI
Age 18 years or over
Time post stroke ≥ 6 months
BTX-A type A (Botox®[1]) treatment for UL spasticity
Muscles injected include elbow flexors
Informed consent obtained from participant

2.3.3 PROCEDURES AND EQUIPMENT

2.3.3.1 Intake and Recruitment

Prior to each Outpatient Spasticity Clinic session, the research team screened the files of patients expected to attend. Those who appeared to be suitable for the study were approached when they attended the Clinic. The aims and procedures of the study were explained and any questions from the patients and/ or their carers were addressed. If patients were willing to participate, they were given the opportunity to either proceed straight away or enroll at their next clinic appointment. When patients were ready to proceed, their eligibility was formally checked (Box 2.2) and if they matched the criteria, they were asked to provide written consent (Appendix 2.2). Study participants were then ready to be assessed.

[1] Allergan Ltd., High Wycombe, UK

2.3.3.2 Assessment

Introduction

As indicated in fig. 2.1, participants were assessed at baseline (week 0) and again at week 4, when the effects were expected to be optimal (Simpson *et al.*, 1996). The rationale for outcome measures selected for this study and details of their procedures will be detailed below. The sequence of assessments was identical for week 0 and week 4 in order to standardise any order effects that might arise. The forms used for the data collection, indicating the order of tests undertaken, are included in Appendix 2.3.

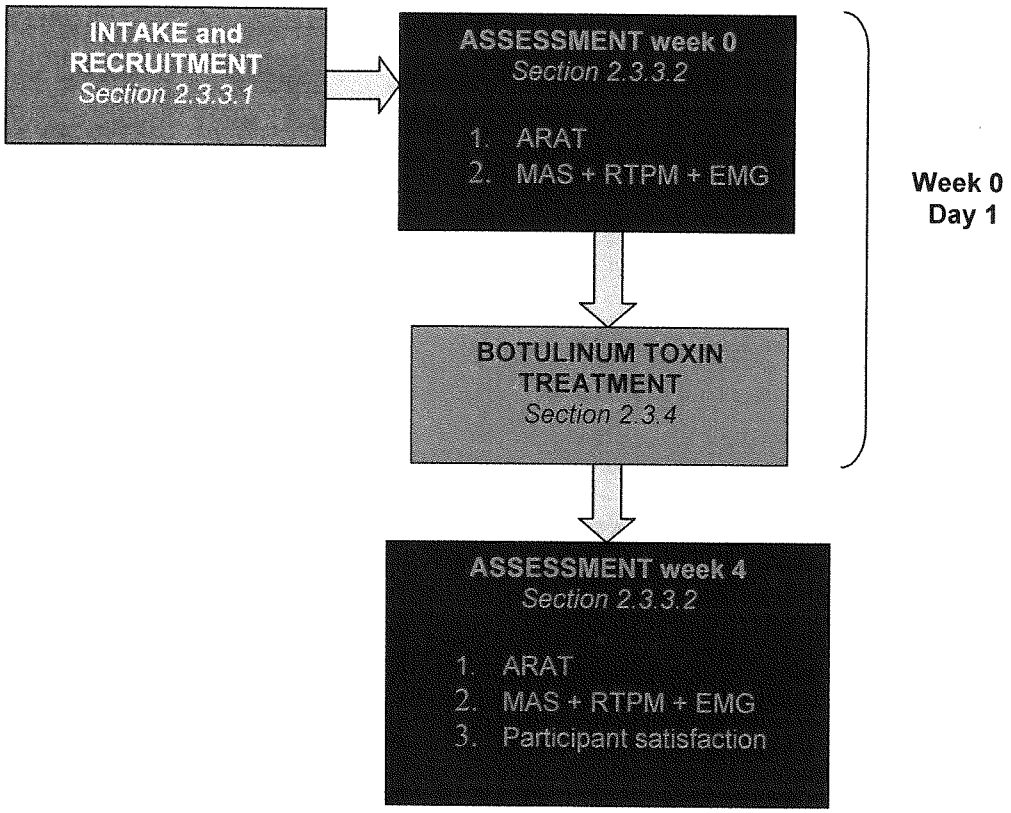


Figure 2.1
Flow diagram of all trial events, from recruitment to completion
ARAT: Action Research Arm Test, MAS: Modified Ashworth scale, RTPM: resistance to passive elbow extension, EMG: elbow flexor EMG, Assessment procedures for weeks 0 and 4 were identical, with the exception of Participant Satisfaction, which was only assessed at week 4.

Modified Ashworth Scale (MAS)

Rationale

The Ashworth Scale (AS, Ashworth, 1964), originally designed to assess resistance to passive movement (RTPM) in patients with Multiple Sclerosis, and the Modified Ashworth scale (MAS, Bohannon and Smith 1987) are probably the most commonly used measures for assessing spasticity in clinical practice (van Wijck *et al.,* 2001). Briefly, the test involves an assessor flexing and then rapidly extending a joint (or vice versa), within the participant's pain-free range of movement (ROM), while the participant remains passive. The resistance encountered is then scored on a scale, outlined in Box 2.3. However, as explained in section 1.2.4.2, both Ashworth scales have been criticised by Pandyan *et al.* (1999, 2001, 2002[b], 2003[b]). Nevertheless, in order to be able to compare the results from this study with similar work, the MAS was included, as with its 6-point ordinal level scale, it was thought to be more sensitive than the original 5-point Ashworth scale.

Protocol

The participant was seated on a chair and instructed to "*relax as much as possible, let me do the work and allow the arm to feel heavy*". The assessor then brought the participant's arm into 90° abduction (or as near as possible while staying within the participant's pain-free ROM) and supported the upper arm in this position, just proximal to the elbow joint. Next, the MAS was carried out (Bohannon and Smith, 1987), with the forearm, placed in neutral between pronation and supination, being supported just proximal to the wrist. The difference with the traditional MAS was that the forearm was not handled directly, but instead via the aluminium handle attached to the force transducer of the measurement device, described below. With the participant being relaxed, the assessor first explored the available pain-free ROM by slowly moving the elbow joint into flexion and then extending it. This manoeuvre was then repeated; once slowly and once rapidly (i.e. with the assessor silently reciting "1001" (Platz and Pinkowski, 1999). The final, brisk manoeuvre represented the actual Ashworth test.

Scoring

The resistance to passive movement, encountered during the final, brisk elbow extension, was scored according to the criteria for the MAS (Box 2.3).

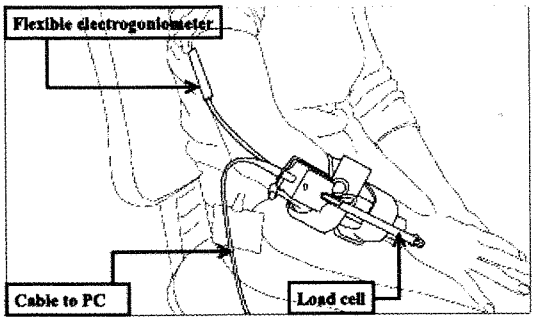
Box 2.3
Scoring criteria for the Modified Ashworth Scale
(Bohannon and Smith, 1987)

Score	Criterion
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a "catch" and release or by minimal resistance at the end of range of motion when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a "catch", followed by minimal resistance throughout the remainder (less than half) of the range of movement (ROM)
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone – passive movement difficult
4	Affected part(s) rigid in flexion or extension

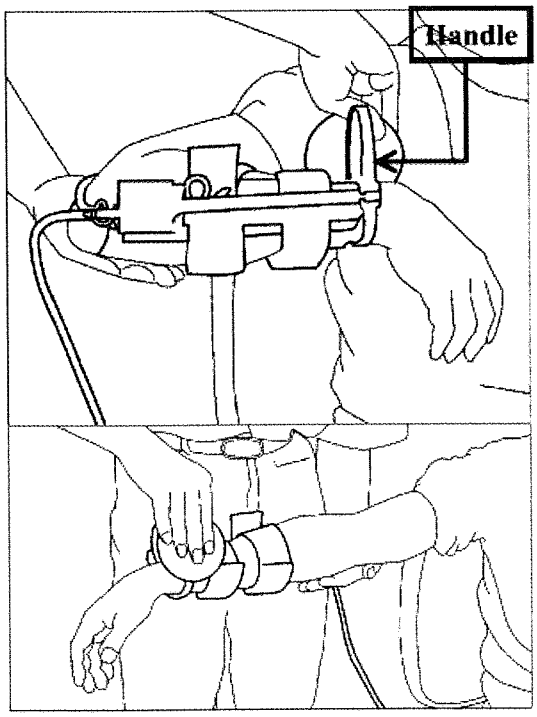
Resistance to Passive Movement (RTPM) and elbow flexor activity (EMG): The DATA System

Rationale

In order to be able to quantify and distinguish between the biomechanical and neurogenic components of RTPM, the Displacement and Torque Analysis (DATA) system developed by Pandyan *et al.* (2001) was used. This instrument was described in section 1.2.4.2 and aspects of its design have been reported by Pandyan *et al.* (2001, 2002[b]). Briefly, this device, illustrated in fig. 2.2, incorporated a purpose-built force transducer, embedded in a cantilever. Onto this cantilever, a handle had been affixed, which was held by the assessor, as he/ she moved the participant's forearm while performing the MAS. The instrument was strapped onto the patient's forearm, leaving the cantilever and the handle free. Thus, the strain gauge measured the force applied by the assessor to the forearm – via the handle - during elbow flexion and extension. Simultaneously, angular displacement of the elbow was measured by a commercially available electrogoniometer (Biometrics Ltd, Gwent, UK), while the electrical activity of the elbow flexors and extensors was registered by means of surface EMG (Bagnoli two-channel with DE 2.1 single differential electrode, Delsys Inc., USA, bandwidth 20-450 Hz, gain 10.000, inter-electrode distance 10 mm, parallel bar electrodes). All data were sampled, simultaneously, with a frequency of 1000 Hz, amplified and stored on a computer for further analysis.



(a)



(b)

Fig. 1. (a) The device used to measure RTPM about the elbow consists of a force transducer and a flexible electrogoniometer (Biometrics Ltd., Gwent, UK), allowing simultaneous measurement of the applied force and passive range of movement. (b) The assessor abducted the humerus to 90° and fully flexed the forearm. The forearm was then rapidly extended.

Figure 2.2
The Displacement And Torque Analysis (DATA) system (Pandyan *et al.*, 2001)
Reprinted from Clinical Biomechanics, Vol. 16, Pandyan, A. D.; Price, C. I. M.; Rodgers, H.; Barnes, M. P.; Johnson, G. R.. Biomechanical examination of a commonly used measure of spasticity, pp 859-865. Copyright (2001), with permission from Elsevier.
Note that EMG equipment is not included in this diagram.

Fig. 2.3 provides an example of typical raw data, showing how "spasticity" may be depicted in three dimensions, i.e. force, angle and EMG. The graph illustrates two manoeuvres: a slow extension of the elbow joint (blue) and a fast extension of the same joint (red), both with the participant being relaxed. The fast manoeuvre replicates the Ashworth Scale. The graph clearly shows the increased EMG response during the fast stretch (red) compared to the slow stretch (blue). During the fast stretch, a greater EMG response was obtained and more force was required to extend the elbow than during the slow stretch. These observations supported the notion of the velocity-dependency of spasticity.

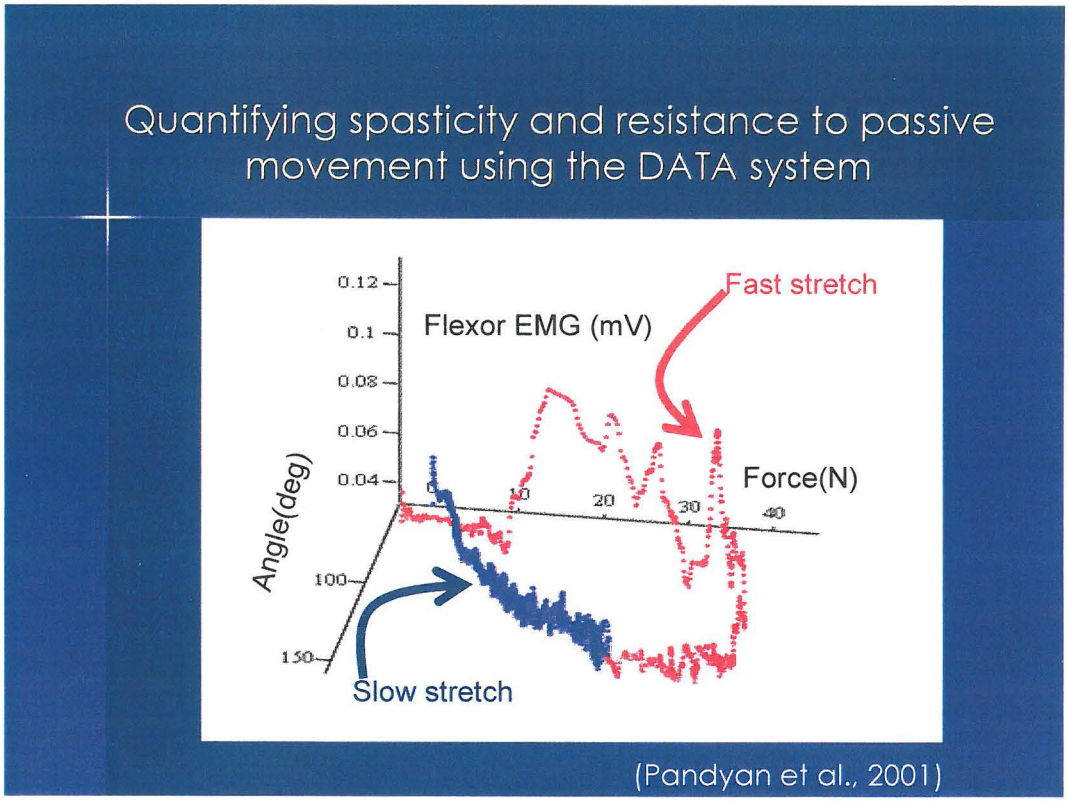


Figure 2.3
Measuring spasticity with the Displacement And Torque Analysis (DATA) system
Spasticity, represented in three dimensions: angular displacement of and force required to extend the elbow joint as well as elbow flexor EMG. The plane formed by the axes of angular displacement and force represents resistance to passive movement. The axis labeled as Flexor EMG represents elbow flexor activity.
Included with permission from Dr. A.D. Pandyan.

At the time of this study, the instrument had only been developed for the elbow joint and thus the quantification of spasticity was limited to this joint. In addition, since the focus of the study was on quantifying RTPM generated by the elbow flexors, only EMG data from this muscle group will be reported - data from the elbow extensors were only used to monitor, prior to data collection, if this muscle group was relaxed.

Validation studies were carried out, which are reported in Appendix 2.4[2]. These were designed to establish the following properties of the measurement system: the construct validity (i.e. whether the device was capable of registering the velocity-dependency of spasticity), accuracy, precision, hysteresis, cross talk and drift of the strain gauge and the electrogoniometer, measured under laboratory conditions. The main findings are listed in table 2.1. In summary, they indicated that the device was capable of measuring the velocity dependency of spasticity, measured as the difference in elbow flexor EMG between slow and brisk elbow extension (fig. 2.3). The strain gauge of the DATA instrument was accurate to 0.40N on average (to 1.0N at worst), while its percentage linearity (4%) and precision (0.42N on average) were sufficiently adequate for the actual clinical tests. The electrogoniometer of the system was accurate to less than 0.5 deg on average (and to less than 1.0 deg at worst), while its percentage linearity (0.5%) and precision (1.3 deg on average), were also more than adequate for the purpose of testing the adult human elbow joint.

Hysteresis was minimal in both the strain gauge and the electrogoniometer. In the former, it constituted less than 3% of the measuring range, while in the latter, it was less than 1%. Although the differences in output from both instruments were significantly different between ascending and descending measurements, both figures were well below the customary 10% of the measuring range. In practical terms, hysteresis was considered to be negligible in both the strain gauge and the electrogoniometer.

With regards to cross talk, for both the strain gauge and the electrogoniometer, the values of the slopes of the regression equations (i.e. -0.001 in both cases) indicated that the impact of moving either instrument through its entire measurement range

[2]This work was the basis for a publication by Pandyan et al., in press (Appendix 6)

would have been approximately zero. In conclusion, cross talk between the strain gauge and electrogoniometer was considered to be negligible.

Regarding drift, measured over a period of more than 2 hours, the strain gauge showed virtually no change in measurement output as a function of time, during which the instrument had been switched on. However, there was some evidence of drift in the electrogoniometer, notably over the first 23 minutes. Whether this was due to temperature drift or stress relaxation was unclear. The difference between output at 0 and 131 minutes (i.e. 3.4 deg) effectively constituted 2.3% of the entire measuring range, which was considered to be negligible.

Table 2.1

Overview of main results from the DATA system calibration.

Full details are reported in Appendix 2.4.

CoV: coefficient of variation

Characteristic	**Conclusions**
Validity: can the system measure Lance's definition?	Yes
Accuracy: ▪ Strain gauge ▪ Electrogoniometer	 Strain Gauge: ▪ Mean Absolute Error = 0.40N (SD 0.22) ▪ Max. Absolute Error = 1.03N ▪ Percentage linearity = 4.22% Electrogoniometer: ▪ Mean Absolute Error = 0.37 deg (SD 0.17) ▪ Max. Absolute Residual Error = 0.73 deg ▪ Percentage linearity = 0.49%
Precision: ▪ Strain gauge ▪ Electrogoniometer	 Strain Gauge: ▪ Mean Precision = 0.42 N ▪ Mean CoV = 3.35% Electrogoniometer: ▪ Mean Precision = 1.29 deg ▪ Mean CoV = -3.42%,
Hysteresis: ▪ Strain gauge ▪ Electrogoniometer	 ▪ Negligible ▪ Negligible
Cross talk	Negligible
Drift: ▪ Strain gauge ▪ Electrogoniometer	 ▪ Negligible ▪ Negligible

Additionally, features related to health, safety and practical issues were evaluated (Appendix 2.4). These showed the system to be safe and easy to apply, although the requirement for post-hoc data analysis rendered the device less suitable for routine clinical application at the time of the study.

Based on these results, it was concluded that the device was safe, valid and practicable and that the strain gauge and electrogoniometer, tested under laboratory conditions detailed in Appendix 2.4, were sufficiently accurate and reliable for the purpose of the study.

Prior to the data collection phase, the assessor was trained by Dr. A.D. Pandyan, who had devised the instrument.

Protocol

Test Administration

After the procedure had been explained, the participant's skin was prepared by cleansing the areas where the electrodes were to be placed with a Steriwipe™. The electrode for the elbow flexors was placed on the midpoint of the midline of the m. biceps brachii. This point was determined by visual inspection and palpation during contraction (Gilmore and Meyers, 1983). The electrode was placed on the anterior aspect of the muscle belly and along the longitudinal line of the muscle fibres (de Luca, 2002). The reference electrode was placed over the epicondylus lateralis of the elbow of the arm to be tested. Next, the component of the device with the force transducer and the distal block of the electrogoniometer were positioned just laterally to the margo posterior of the ulna and attached, using Velcro straps, to the dorsal aspect of the participant's forearm. The proximal endblock of the electrogoniometer was attached, in line with its distal block, to the dorsal aspect of the participant's upper arm by means of double-sided medical tape. The quality of the signals was checked prior to data collection. The procedure then followed that for the MAS, described above. Prior to testing, the EMG signals were monitored to check whether the elbow flexors and extensors were indeed relaxed, as indicated by a minimum amplitude. If this were not the case, the instruction was repeated and the assessor waited until relaxation had been achieved. Next, the MAS (Bohannon and Smith, 1987) was carried out, as indicated above. The difference with the

traditional MAS was that the forearm was not handled directly, but instead via the aluminium handle attached to the force transducer (fig. 2.2). With the participant being relaxed, the assessor first explored the available pain-free ROM by slowly moving the elbow joint into flexion and then extending it. This manoeuvre was then repeated; once slowly (to measure RTPM and EMG during slow elbow extension) and once briskly (to replicate the MAS). The differences in EMG and RTPM between these two conditions would enable the velocity-dependency of these parameters to be determined.

The aim was to carry out the brisk movement once only in order to avoid data being confounded by repetitive testing which, according to Hill (1986, cited by Walsh, 1992) might reduce thixotropy. Additionally, repeated testing might enable participants to predict the manoeuvre, which in turn might affect their reflex response (Cathers *et al.*, 1996). However, in some cases where the participant was unable to relax the muscle groups being tested (as determined on the basis of the raw EMG signal, which was being monitored on-line) or had not understood the instructions, it was necessary to repeat the rapid elbow extension. Since Pandyan *et al.* (2001), had not found any significant differences between three repeated trials of the MAS taken in quick succession, using the same methodology involving stroke patients, no more than three trials were carried out at any one session. Data from the last trial, including the clinical Ashworth score, were noted and used for the analysis.

Scoring

The data were stored and analysed *post hoc*, as described in section 2.3.5.

Action Research Arm Test

Rationale

The Action Research Arm Test (ARAT, Lyle 1981) was chosen for this study as its psychometric properties are favourable and it is the only dedicated upper limb function test in the top-five of the most commonly used outcome measures in neurological rehabilitation (van Wijck *et al.,* 1999[3], 2001) and thus enables

[3] These publications are listed in Appendix 6.

comparison with similar work. The ARAT is based on the Upper Extremity Function Test (Carroll, 1965), which Lyle rendered more concise and efficient through Gutmann scaling.

Numerous studies have reported the generally robust psychometric properties of the ARAT, including its validity (de Weerdt and Harrison 1985; Hsieh *et al.,*1998; Broeks *et al.,* 1999; Platz., 2004), reliability (Lyle 1981; Wagenaar *et al.,* 1990; Hsieh *et al.,* 1998; Platz, 2004; Platz and Pinkowski, 1999; van der Lee *et al.,* 2001a) and responsiveness (de Weerdt and Harrison 1985; van der Lee 2001a; Hsueh and Hsieh 2002; Kwakkel *et al.,* 2002). However, when a team of clinicians[4] attempted to use the ARAT in clinics distributed over three different countries, they discovered considerable variation in the administration and scoring of the test[5]. It became apparent that the original description of the ARAT was insufficiently detailed for it to be replicated in exactly the same way by different assessors. In stark contrast to the number of papers on the reliability of ARAT scoring, there did not appear to be any literature on the reliability of the ARAT *administration* at the time. Therefore, as part of the DRAMA Telematics Applications Programme Project (Developments in Rehabilitation of the Arm – a Multimedia Approach), of which the author was a member, a set of standard guidelines were developed (Platz and Pinkowski, 1999; Platz *et al.,* 2005a[6]). Platz *et al.* (2005b[7]) found inter-rater reliability and test-retest reliability of these guidelines to be very high (ICC = 0.998) and comparable to those reported by the single-centre studies already published. Furthermore, Patel (2003) demonstrated that these standard guidelines resulted in a significant reduction in the errors as well as inter-rater variation in test administration when compared with Lyle's original documentation.

Protocol and Equipment

The ARAT

[4] DRAMA: Developments in Rehabilitation of the Arm – a Multimedia Approach, Telematics Applications Programme Project DE4203.

[5]The differences between some of these permutations were not trivial, e.g. according one interpretation, a test item involved moving an object across midline, whereas according to another interpretation, the same test item required the object to be moved forward, while remaining on the same side of the patient's midline. It is obvious that these two interpretations involved different perceptuo-motor tasks.

[6] This publication is listed in Appendix 6.

[7].This publication is listed in Appendix 6.

The ARAT table described by Lyle (1981) consists of a metal trolley, 92 cm x 45 cm x 83 cm high, constructed of slotted iron, and with a shelf 93 cm x 10 cm positioned 37 cm above the table top of the trolley (fig. 2.4). The participant is seated on a chair, 44 cm above floor level. The trolley is positioned close to the participant's chest, with its midline in line with the participant's midline. Lyle's guidelines indicated that test items were to be "placed appropriately for the side to be tested", but did not specify any further precise starting or end position for most of the tasks. The test is divided into four subtests (i.e. Grasp, Grip, Pinch, Gross movement), each of which consists of a number of different items; 19 in total (App. 2.3). Tasks involve different sizes of blocks and tubes, as well tumblers, ball bearings, a cricket ball and a sharpening stone. For the first three subtests, the participant is asked to pick and place a number of different objects and place them on a designated location. The fourth subtest requires the participant to touch the head in different places.

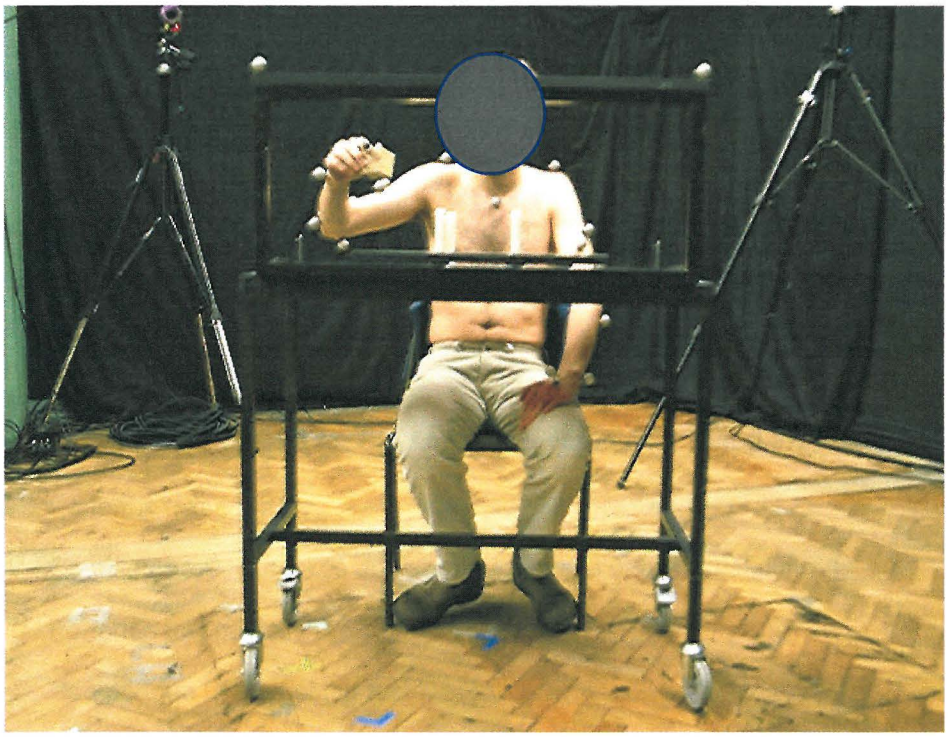


Figure 2.4
The Action Research Arm Test
Reflective markers were placed on the participant as well as on the table to enable 3D motion analysis using the Vicon system
(ViconPeak, Oxford, UK. http://www.vicon.com/contact/)

Test Administration

The complete protocol of administering and scoring the ARAT is included in App. 2.3. The dimensions of all the test items can be found in Platz *et al.* (2005).

For each participant, both upper limbs were tested: according to the Platz and Pinkowski (1999) guidelines, the task was carried out with the non- or less affected side first, in order for the participant to obtain the correct image of the task. When the participant demonstrated that the task was understood, it was then carried out with the (more) affected side. An additional specification was that the starting position for each task (except subtest gross movement) was with the tested arm placed on the table top. The participant was allowed to rest between the tasks, but did not receive any form of therapeutic intervention in between tasks. Additional specifications, approved by Dr. Lyle (personal communication, 7/99) were that the objects listed under each item for each subtest had to be presented one at a time. There was no quantitative time limit for performing the test.

Scoring

Scoring was not based upon a comparison between affected and non- or less affected side, but instead on what is considered to be "normal". Finally, Dr. Lyle (personal communication, 7/99) explained that the patient was permitted to practice, but that the score was based on one trial only. Box 2.4 lists the scoring criteria for the ARAT.

Box 2.4
Scoring criteria for the Action Research Arm Test (Lyle 1981)

Scoring:	
3:	Performs test normally
2:	Completes test, but takes abnormally long time or has great difficulty
1:	Performs test partially
0:	Can perform no part of the test

Participant Satisfaction

Rationale

In order to gauge the extent to which participants felt their treatment had been effective, a simple rating scale was used at Week 4.

Protocol

A simple questionnaire was used to gauge the participant's opinion on the effects of the intervention (Box 2.5). In addition, participants were also asked whether they had experienced any adverse reactions.

Box 2.5
Participant satisfaction scale

Since your last assessment, has your condition (please tick):

- **Remained the same** ☐
- **Got worse:** ☐
  - A little ☐
  - Moderately ☐
  - A lot ☐
- **Got better:** ☐
  - A little ☐
  - Moderately ☐
  - A lot ☐

2.3.4 BOTULINUM TOXIN TYPE-A TREATMENT

Botulinum toxin type-A was administered by clinicians, not otherwise involved in the study, as per usual clinic procedures. All participants were given Botox® (Allergan Ltd, High Wycombe, UK). Each vial of the toxin was reconstituted in 5 ml Normal Saline. No EMG guidance was used in this procedure.

2.3.5 DATA REDUCTION AND ANALYSIS

Speed

Given the fact that the spasticity measurement device did not control the rate of displacement of the joint, together with the notion that spasticity is a velocity dependent phenomenon (Lance, 1980), it was necessary to calculate the speed of

elbow extension *post-hoc.* Average speed was calculated by dividing the angular displacement by the time taken to complete the trajectory, which commenced at maximum elbow flexion and ended at maximum elbow extension. These points were determined visually from the elbow displacement graph, displaying the raw data (see fig. 2.5 for an example), by moving the cursor sample-by-sample by hand on several occasions until the correct data points had been identified. In cases where the speed during the "slow" trial actually turned out to be faster than the "fast" trial, the trial was disqualified and omitted from the analysis.

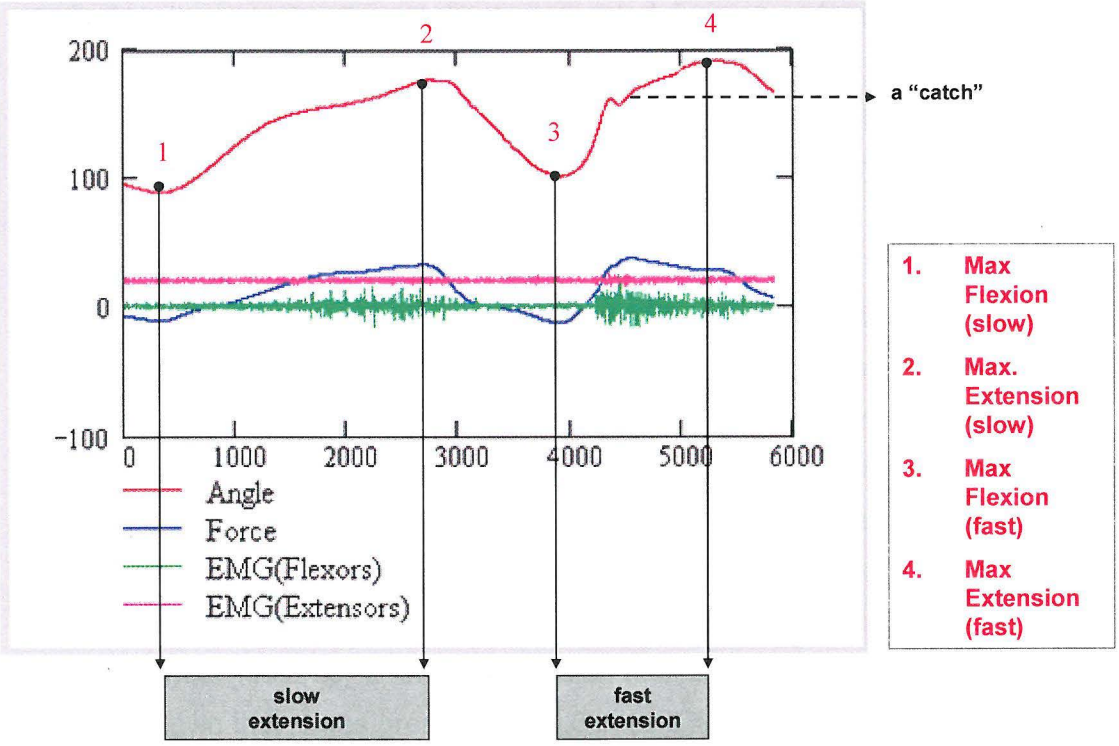


Figure 2.5
An example of typical raw data, collected with the DATA system during slow and fast passive elbow extension.
Angle (deg): elbow displacement, Force (N): force applied by the assessor to the participant's arm, EMG (Flexors, μV): surface EMG from the elbow flexors, EMG (Extensors, μV): surface EMG from the elbow extensors. All data were sampled simultaneously with a frequency of 1000 Hz. Resistance to passive movement (RTPM), EMG and average speed were calculated from maximum elbow flexion to maximum elbow extension for both the slow (1->2) and the fast (3->4) movement.

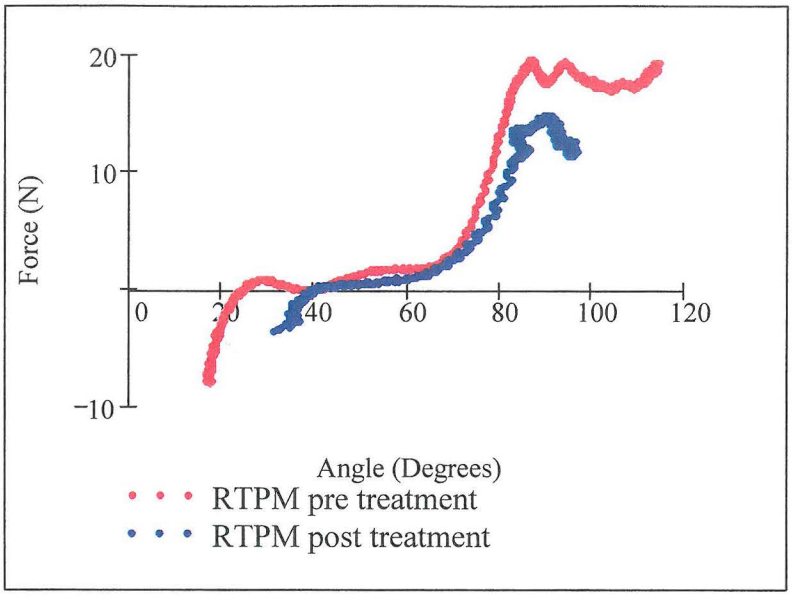
EMG

The raw surface EMG signal of the elbow flexors was collected over the trajectory from maximum elbow flexion until maximum elbow extension (as detailed in the section on Speed). The data were notch filtered and smoothed by means of a root mean square procedure (Mathcad v.11, MathSoft Co.). Average power of the signal was used as the dependent variable and this was calculated using a Mathcad procedure (Mathcad Signal Processing Extension Pack, MathSoft Engineering and Education Inc., 2001), based on Stearns and David (1998).

Given the volatility of the EMG signal, a common technique is to normalise the amplitude with respect to the amplitude generated during a certain percentage of the maximum voluntary isometric contraction of the same muscle group (De Luca, 2002). Although this procedure was considered, it was omitted, given the uncertainty regarding the effect of BTX-A on muscle force (Simpson *et al.,* 1996).

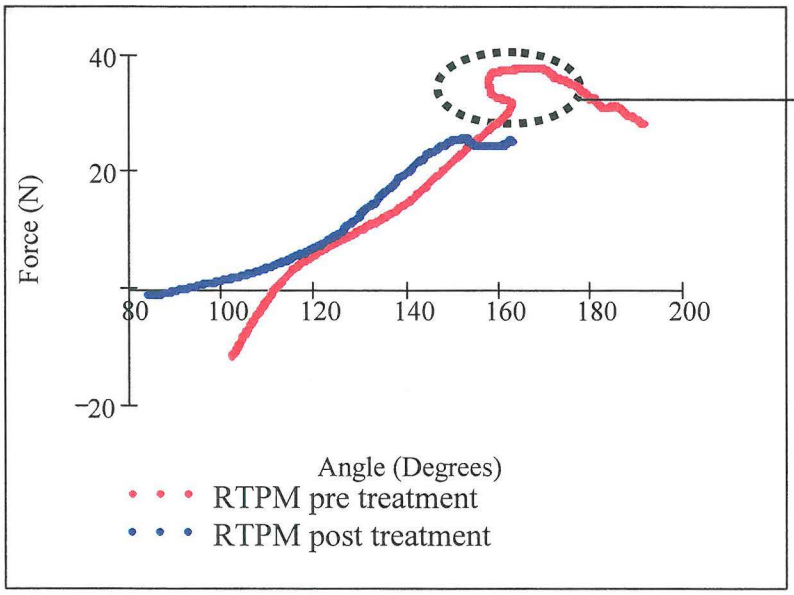
RTPM

RTPM was also calculated over the trajectory from maximum elbow flexion to maximum elbow extension, which was determined as for the calculation of speed (see above). RTPM was computed as the slope of the linear regression line through the force-angle graph (i.e. the force applied to the participant's forearm during elbow displacement), using Mathcad v.11 (MathSoft Co.) and represented the stiffness encountered by the assessor during the MAS, while r^2 provided an indication of the goodness of fit. Fig.2.6 shows two examples of different curve shapes. Despite some non-linear features, a linear regression technique was used, since previous work had shown that r^2 was greater than 0.6 in 90.6% of the curves, thus classifying the shapes as linear (Pandyan et al., 2001). Since linear regression analysis had also been used a study with non-impaired controls (Barnaby, 2002), this technique would enable the data from the current study to be compared with similar work.



Pre BTX-A treatment
RTPM = 0.26 N/deg (r^2 = 0.922)
Speed = 74 deg/s

Post BTX-A treatment
RTPM = 0.27 (r^2 = 0.895)
Speed = 74 deg/s



Pre BTX-A treatment
RTPM = 0.46 N/deg (r^2 = 0.776)
Speed = 66 deg/s

Post BTX-A treatment
RTPM = 0.38 (r^2 = 0.966)
Speed = 78 deg/s

Fig. 2.6
Two examples of typical force-angle curves, obtained with the DATA system at a sampling frequency of 1000 Hz.
BTX-A: botulinum toxin type-A.
The slope of the linear regression line through each curve represented RTPM (resistance to passive movement, N/deg), while r^2 represented the goodness-of fit.
The second curve features a "catch".

Modified Ashworth Score

The MAS resulted in a single score for each participant. Since this scale yields ordinal level data, the median, minimum, maximum and range were calculated for the cohort. Inter-quartile ranges were not calculated, as these were not considered to be clinically meaningful. MAS score "1+", was entered into the database as "1.5".

Action Research Arm Test

All item scores were summated for each participant to produce their total score, as per original protocol. With the ARAT yielding ordinal level data, the median, inter-quartile range (iqr), minimum and maximum were computed from the total scores to produce cohort data.

Participant satisfaction

From the single data point from each participant at Week 4, the median, minimum, maximum and inter-quartile range was compiled for the cohort.

Inferential statistics

All hypotheses were 2-tailed and alpha was set at 0.05. In order to test for normality, Shapiro-Wilks test was used, as it tends to be more accurate than the Kolmorogov-Smirnov test (Field, 2000). Since the study had a same-subject design with two repeated measures, related t-tests were used to compare ratio level data (i.e. $RTPM_{fast}$, EMG_{fast} and GS), provided that the requirements of normality were met. The Wilcoxon matched pairs signed ranks test was used for ordinal level variables (i.e. ARAT and MAS), or for ratio level variables that were not normally distributed. SPSS version 12 (SPSS Inc.) was used for the statistical analysis.

2.4 RESULTS

This section is structured according to the study aims set out in section 2.2. For each of the outcome measures, descriptive results will be presented first, followed by inferential statistics. The results pertaining to the speed of elbow extension during the MAS are presented first, in order to determine the validity of the trials. Part of these results have been reported in previous publications (Pandyan *et al.*, 2001, 2002a, 2002b)[8].

2.4.1 SAMPLE

A total of 25 participants were recruited; 11 in a pre-pilot phase and 14 in the actual pilot study. The pre-pilot phase was required for the research team to fine-tune the test protocols, become proficient at using the measurement device and solve any technical problems with the DATA system. Although data were collected, they only served to check the quality of the data acquisition processes, were not used for the analysis. Therefore, this initial phase will not be further described. Once the technical issues had been resolved and the methodology had been finalised, the actual pilot study began.

Fourteen participants were included in the actual pilot study. There were no drop-outs. Relevant demographic characteristics are described in table 2.2. The Bamford stroke classification (1991) was used to categorise the various types of stroke. In summary, 3 participants had a haemorrhagic stroke, 10 had an ischaemic stroke and in 3 cases, information about the specific type of stroke was not available. In order to assess whether a participant had a contracture of the soft tissues around the elbow, the research therapist passively extended this joint to the maximum, but painfree, range of movement (ROM) and held this position for 1 minute. The joint was then released and, immediately after, the position of the joint was measured with a standard clinical goniometer. Table 2.2 shows that mean passive range of movement (PROM) of the elbow was 134.4 deg (SD 25.7, range 95 deg -165 deg), and that none of the participants had full elbow extension.

[8] These publications are listed in Appendix 6.

Participants were also asked about concurrent forms of treatment, i.e. whether they had a hand splint and if they were taking part in physiotherapy or occupational therapy. Their response was simply noted as a "yes" or "no"; participants were not asked any details about the intensity or content of their therapy input.

Table 2.2
Characteristics of the study participants
PID: Participant ID, BTX-A: botulinum toxin type-A. Length BTX-A: length of time participants had received BTX-A. PACI, HAE, TACI: stroke classification according to the Bamford classification (1991); Mv: missing value. Dom. Hand: dominant hand, Aff. hand: primarily affected hand. Elbow ROM: Elbow range of movement. Con.Ther.: participant receiving physiotherapy or occupational therapy in conjunction with BTX-A.
S: hand splint: Y= yes, N=no.

PID	Sex	Age (years)	Time post stroke (years)	Length BTX-A (years)	Stroke type	Dom. hand	Aff. hand	Elbow ROM (deg)	Con Ther.	S
A6	F	62	1.0	0.3	PACI	R	R	150	Y	Y
A5	F	38	2.7	0.8	PACI	R	L	142	Y	N
A3	M	58	3.3	2.8	HAE	L	R	155	N	Y
A7	M	64	4.0	1.2	PACI	R	L	96	N	Y
C2	F	54	4.9	4.0	TACI	R	L	165	N	Y
C1	F	56	8.0	0.3	Mv	R	L	165	Y	Y
C6	F	26	3.5	3.1	TACI	L	R	140	Y	N
C0	M	61	2.8	2.5	HAE	R	R	155	Y	Y
B5	M	61	5.4	3.0	TACI	R	R	138	Y	Y
B7	M	63	5.0	0.3	TACI	R	R	155	Y	Y
B8	M	62	1.0	0.5	TACI	R	L	110	N	Y
C5	M	84	1.8	1.2	PACI	R	L	105	Y	Y
B9	M	63	4.1	3.0	TACI	mv	L	95	Y	Y
C3	F	47	5.0	0.5	HAE	R	R	110	Y	N
Mean		**57**	**3.8**	**1.7**				**134.4**		
SD		**14**	**1.9**	**1.3**				**25.7**		
Min		**26**	**1**	**0.3**				**95**		
Max		**84**	**8**	**4**				**165**		

2.4.2 BOTULINUM TOXIN TYPE-A TREATMENT

For each participant, the dosage and injection sites are listed in Table 2.3.

Table 2.3
Botulinum toxin treatment (Botox®, Allergan Ltd, High Wycombe, UK) for each study participant.
Dosage per injection site and cumulative dosage (MU: mouse units). Pec: mm. Pectorales, Bic: m. biceps brachii, Brad: m. brachioradialis, FAFL: Forearm flexor compartment, Then: thenar, Cum: cumulative dosage.

Participant ID	Pec (MU)	Bic (MU)	Brad (MU)	FAFL (MU)	Then (MU)	Cum (MU)
A6	0	25	0	115	0	140
A5	0	50	0	50	0	100
A3	0	25	25	120	0	170
A7	0	25	25	90	0	140
C2	0	25	0	100	0	125
C1	15	50	30	50	0	145
C6	0	300	200	0	0	500
C0	0	40	0	60	0	100
B5	0	80	30	90	10	210
B7	0	80	50	58	12	200
B8	0	75	50	75	0	200
C5	0	75	85	75	0	235
B9	0	80	40	80	0	200
C3	0	60	30	120	0	210
Mean	**1**	**71**	**40**	**77**	**2**	**191**
SD	**4**	**70**	**52**	**33**	**4**	**99**
Min	**0**	**25**	**0**	**0**	**0**	**100**
Max	**15**	**300**	**200**	**120**	**12**	**500**

2.4.3 SPEED OF ELBOW EXTENSION

Table 2.4 shows that the speed during fast elbow extension (i.e. the MAS) was in fact higher than during the slow movement, both at baseline and at Week 4, for all participants bar one (B7). Therefore, the data from this participant were deemed invalid and omitted from the analysis. Given the considerable variation in absolute speed between participants, the ratio of "slow" to "fast" (as opposed to their difference) was calculated to compare the two conditions. On average, the slow trial was carried out at about 50% of the speed of the fast trial, both at baseline and after treatment, although the high standard deviation and range for each condition indicate there was considerable variability, both within and between participants. The coefficient of variation however, suggests that the proportion of variation in relation to the average speed in each condition was comparable (range 0.77-0.83).

Although the speed of the slow elbow extension at baseline (mean 20.9 deg/s, SD 17) was lower than at re-assessment (mean 26.1 deg/s, SD 21.7), this difference was not statistically significant[9] (95% CI: -18.0 to 6.1 deg/s, t=-1.079, df=12, p=0.30). Similarly, the speed of fast elbow extension at baseline (mean 55.67 deg/s, SD 42.7) was lower than at re-assessment (mean 65.4 deg/s, SD 54.2), but again this difference was not statistically significant (95% CI: -40.3 to 19.8 deg/s, t=-0.741, df=12, p=0.47). In contrast, the difference between fast and slow was significantly different, both at baseline (95% CI: 22.5 to 54.0 deg/s, t=5.277, df=12, p<0.001,) and at re-assessment (95% CI: 21.0 to 64.0 deg/s, t=4.306, df=12, p=0.001).

Table 2.4
Mean speed (deg/s) during slow and fast passive elbow extension
The fast movement represents the Modified Ashworth Scale. Measures taken at baseline (pre) and 4 weeks after treatment (post) botulinum toxin type-A treatment. Note that for B7, the "fast" trial is actually slower than the "slow" trial, both before and after treatment.

Participant ID	Mean speed (deg/s) *slow* (pre)	Mean speed (deg/s) *fast* (pre)	*Ratio slow/fast (%) (pre)*	Mean speed (deg/s) *slow* (post)	Mean speed (deg/s) *fast* (post)	*Ratio slow/fast (%) (post)*
A6	37.3	66.4	*56.17*	19.9	78.6	*25.32*
A5	23.7	68.5	*34.60*	38.9	122.5	*31.76*
A3	14.0	63.7	*21.98*	76.6	177.0	*43.28*
A7	70.4	178.7	*39.40*	60.7	103.2	*58.82*
C2	20.9	58.1	*35.97*	40.6	146.8	*27.66*
C1	16.4	50.9	*32.22*	12.6	36.6	*34.43*
C6	4.6	5.3	*86.79*	3.1	6.1	*50.82*
C0	25.7	85.6	*30.02*	34.9	59.2	*58.95*
B5	11.6	48.1	*24.12*	18.5	63.9	*28.95*
B7	19.9	8.5	*234.12*	14.2	11.5	*123.48*
B8	20.6	54.4	*37.87*	12.1	52.7	*22.96*
C5	3.0	12.4	*24.19*	3.0	7.4	*40.54*
B9	19.7	43.7	*45.08*	17.6	30.7	*57.33*
C3	5.4	34.9	*15.47*	12.2	18.8	*64.89*
Mean	**20.9**	**55.7**	***51.3***	**26.1**	**65.4**	***47.8***
SD	**17.0**	**42.7**	***55.5***	**21.7**	**54.5**	***26.0***
CoV	**0.81**	**0.80**	***NA***	**0.8**	**0.8**	***NA***
Min	**3.0**	**5.3**	***15.5***	**3.0**	**6.1**	***23.0***
Max	**70.4**	**178.7**	***234.1***	**76.6**	**177.0**	***123.5***

[9] Speed data were normally distributed and as they presented ratio level data, Student T-tests were used to analyse the differences.

2.4.4 EFFECTS OF BOTULINUM TOXIN TYPE-A

2.4.4.1 Effects on RTPM

Modified Ashworth Scale (MAS)

MAS scores for passive elbow extension are presented in table 2.5 and fig. 2.7. These data show that none of the participants in the study presented with either normal tone (MAS=0) or a rigid elbow joint (MAS=4) at any point in time. Before treatment, most participants presented with a MAS of 1+. Following treatment, the median MAS decreased (fig. 2.7), although the median change was 0 points. Although six participants did improve, the other eight did not, which placed the middle of the distribution of the change scores at 0. The maximum benefit obtained from BTX-A on the MAS was a reduction of 1 point. When testing for significance (Hypothesis H_0A), the difference in MAS between baseline and after treatment turned out to be statistically significant (Z=-2.271, p=0.023).

Table 2.5
Modified Ashworth Scale (MAS): before and 4 weeks after treatment with botulinum toxin type-A
A negative change in MAS indicates an improvement. For the purpose of the analysis, MAS "1+" was converted to "1.5".

Participant ID	MAS before	MAS after	Change in MAS
A6	1+	1+	0
A5	1+	1	-0.5
A3	1+	1+	0
A7	1+	1	-0.5
C2	1+	1	-0.5
C1	1+	1+	0
C6	2	2	0
C0	2	1+	-0.5
B5	2	2	0
B7	3	3	0
B8	3	2	-1
C5	3	2	-1
B9	3	3	0
C3	3	3	0
Median	**2**	**1.75**	**0**
Min	**1+**	**1**	**0**
Max	**3**	**3**	**-1**

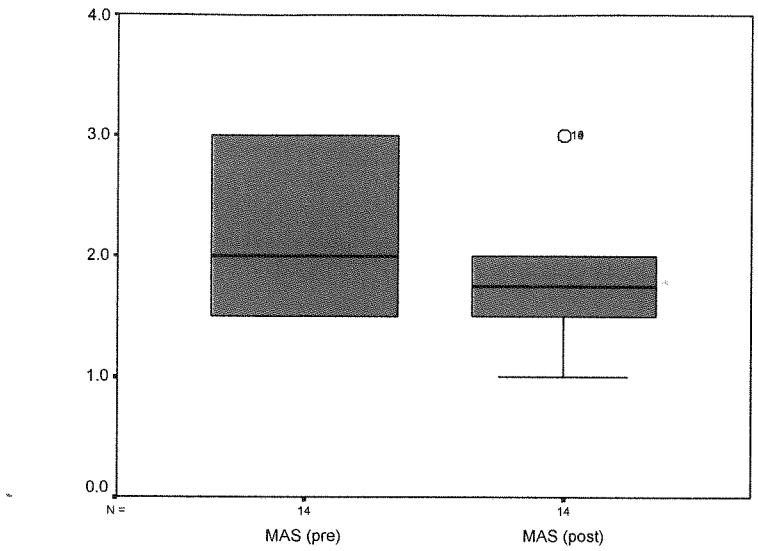


Figure 2.7
Box plot of the Modified Ashworth Scale (MAS) before and 4 weeks after treatment with botulinum toxin type-A
A higher score indicates greater resistance to passive movement.

Resistance to passive elbow extension ($RTPM_{fast}$)

Table 2.6 and fig. 2.8 show that $RTPM_{fast}$ (i.e. during the MAS) increased slightly by 0.03 N/deg (SD 0.31), from a mean value of 0.45 N/deg (SD 0.33) at baseline to 0.48 N/deg (SD 0.37) after treatment. The large standard deviation suggests considerable variability between participants. In six of the 14 participants, RTPM decreased following BTX-A, but in seven cases, $RTPM_{fast}$ actually increased.

Prior to testing hypothesis H_0B1, the Shapiro-Wilks test was used to test the normality of the distribution of the RTPM data. At baseline, the distribution was significantly different from normal (p=0.02), although at Week 4, this was not the case (p=0.36). The Wilcoxon matched pairs signed ranks test was used and the increase in RTPM from baseline to Week 4 was not significant (Z=-0.175, p=0.86).

Table 2.6
Elbow flexor EMG_{fast} (μV)) and Resistance to Passive Movement ($RTPM_{fast}$, N/deg) during passive elbow extension : before and 4 weeks after treatment with botulinum toxin type-A

Note that for B7, average speed of the "fast" condition was slower than that of the "slow" condition, both before and after treatment (table 2.4). Therefore, the quantitative spasticity data for this participant were deemed invalid and omitted from the analysis.

Participant ID	Elbow flexor EMG_{fast} (μV) (pre)	$RTPM_{fast}$ (N/deg) (slope (r^2)) (pre)	Elbow flexor EMG_{fast} (μV) (post)	$RTPM_{fast}$ (N/deg) (slope (r^2)) (post)	Elbow flexor EMG_{fast} (μV) (post-pre)	$RTPM_{fast}$ (N/deg) (post-pre)
A6	3.82	0.46 (0.78)	2.47	0.38 (0.97)	-1.35	-0.08
A5	2.37	0.42 (0.86)	2.53	0.15 (0.95)	0.16	-0.28
A3	3.61	0.43 (0.67)	3.15	0.16 (0.88)	-0.46	-0.28
A7	7.29	0.33 (0.97)	4.25	-0.12 (0.66)	-3.03	-0.45
C2	2.81	0.09 (0.61)	2.85	0.27 (0.91)	0.04	0.19
C1	3.38	0.27 (0.95)	2.95	0.27 (0.93)	-0.43	0.01
C6	2.43	0.18 (0.29)	2.19	0.20 (0.50)	-0.24	0.02
C0	2.00	0.42 (0.98)	2.59	0.61 (0.95)	0.59	0.19
B5	2.43	0.14 (0.94)	2.05	0.85 (0.99)	-0.38	0.71
B7	.	.	.		.	.
B8	4.95	1.19 (0.99)	3.55	1.01 (0.88)	-1.40	-0.18
C5	5.59	0.60 (0.91)	2.61	0.83 (0.78)	-2.99	0.24
B9	5.22	0.33 (0.80)	4.68	0.63 (0.88)	-0.55	0.31
C3	2.37	1.06 (0.96)	3.46	1.00 (0.97)	1.10	-0.06
Mean	**3.71**	**0.45 (0.82)**	**3.03**	**0.48 (0.86)**	**-0.69**	**0.03**
SD	**1.60**	**0.33 (0.20)**	**0.78**	**0.37 (0.14)**	**1.23**	**0.31**
95% CI	**2.74 – 4.68**	**0.25 – 0.66**	**2.55 – 3.50**	**0.26 – 0.70**	**-1.43 – 0.06**	**-0.16 – 0.21**
Min	**2.00**	**0.09 (0.29)**	**2.05**	**-0.12 (0.50)**	**-3.03**	**-0.45**
Max	**7.29**	**1.19 (0.99)**	**4.68**	**1.01 (0.99)**	**1.10**	**0.71**

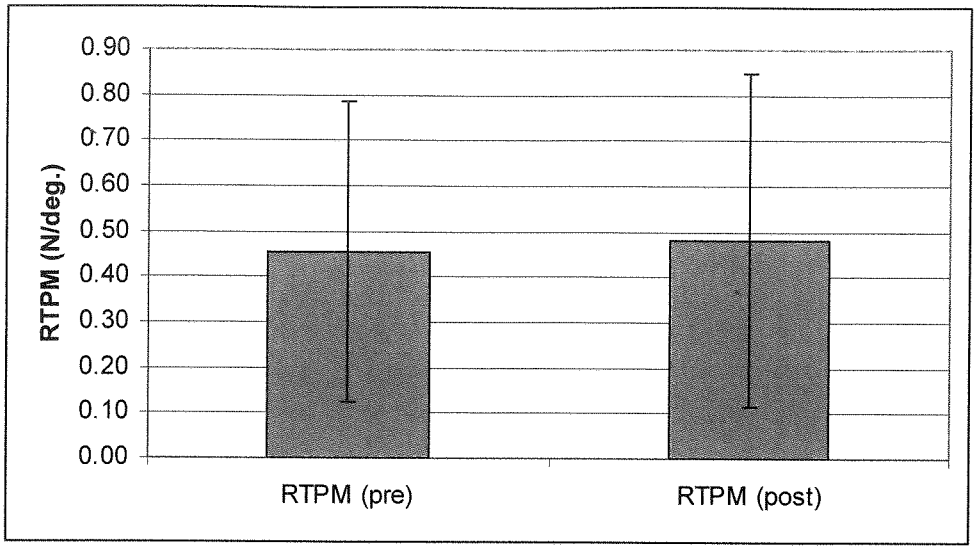


Figure 2.8
Resistance to passive elbow extension ($RTPM_{fast}$, N/deg) at baseline and 4 weeks after treatment with botulinum toxin type-A: mean and SD.

$RTPM_{fast}$- $RTPM_{slow}$ before versus $RTPM_{fast}$- $RTPM_{slow}$ after treatment

Appendix 2.4 gives an overview of RTPM during slow and fast passive elbow extension, both before and after BTX-A. The difference in mean RTPM between fast and slow trials, a measure of the velocity dependency of RTPM, reduced from 0.12 N/deg (SD 0.30) at baseline to 0.06 N/deg (SD 0.25) four weeks after treatment. In order to test whether this difference was significant (hypothesis H_0B2), the Wilcoxon matched pairs signed ranks test was used, as the RTPM fast-slow pre data were not normally distributed (Shapiro-Wilks test, p=0.015). The difference was not significant (Z=-0.245, p=0.81).

2.4.4.2 Effects on spasticity

Comparing mean elbow flexor EMG during the MAS before and after treatment, it can be seen from table 2.6 and fig. 2.9 that this decreased by 0.69 μV (SD 1.23), from a mean of 3.71 μV (SD 1.60) to 3.03 μV (SD 0.78). Again, there was considerable variability, as indicated by the high standard deviation. Whilst EMG_{fast} decreased in eight of the fourteen participants after treatment, it increased in four.

Prior to testing hypothesis H_0C1, the Shapiro-Wilks test was used, which indicated that the EMG data were normally distributed at baseline (p= 0.075), as well as after

treatment (p=0.244). The difference in elbow flexor EMG_{fast} between baseline and after treatment was not statistically significant (95% CI: -1.43 to 0.06 μV, t=2.013, df=12, p=0.07), although there was a trend to suggest that elbow flexor EMG_{fast} decreased following treatment with BTX-A.

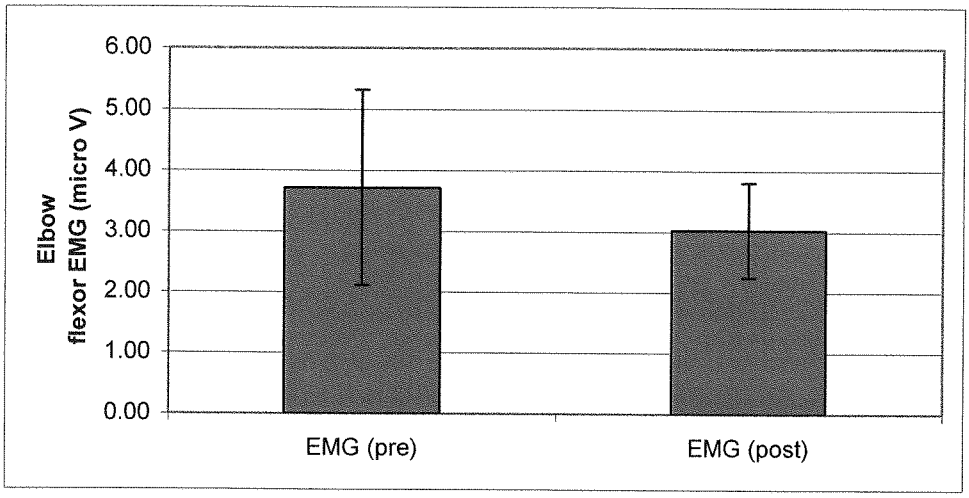


Figure 2.9
Elbow flexor EMG_{fast} (μV) before and 4 weeks after treatment with botulinum toxin: mean and SD.

EMG_{fast}- EMG_{slow} before versus EMG_{fast}- EMG_{slow} after treatment

Exploring the effects of BTX-A on the difference between EMG in the fast and slow condition, Appendix 2.4 shows that this difference was smaller after treatment (mean 0.41 μV, SD 0.39) than before (mean 0.77 μV, SD 0.83), although the high standard deviation suggests considerable inter-subject variation. Both the distributions of EMG_{fast}- EMG_{slow} before and EMG_{fast}- EMG_{slow}_after treatment were not significantly different from normal (p=0.09 and p=0.22, resp.), so that a T-test could be used. This showed that the reduction was not statistically significant (Hypothesis H_0C2: 95% CI: -1.08 to 0.81 μV, t=1.669, df=12, p=0.12).

2.4.4.3 Effects on upper limb function

Action Research Arm Test

Results pertaining to arm function are presented in table 2.7 and fig. 2.10. At baseline, 11 of the 14 participants could not perform any of the manipulation tasks at all; they were only able to score points in the "gross movement" subtest, resulting in a median total ARAT score of 3 (iqr 1.5). Following treatment, this improved slightly to 3.5 (iqr 3.25), although the median change was 0 points. The performance of one participant deteriorated (albeit by 1 point), improved in six, but did not change in seven participants. Three participants who had not been able to perform any of the reach-and-grasp tasks of the ARAT (ARAT a, b, c) before the intervention (i.e. A3, C1 and B8), were now able to perform part of some of the tasks, with participant A3 managing to carry out some of the fine finger dexterity tasks (ARATd). Comparing before with after treatment (Hypothesis H_0D), the difference in total ARAT scores was statistically significant (Z= -1.98, p=0.048).

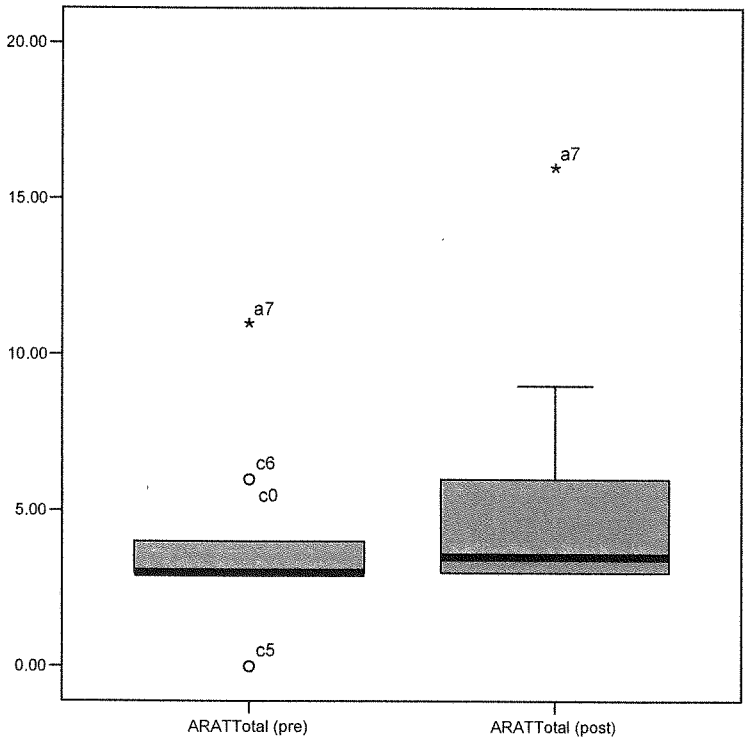


Figure 2.10
Performance on the Action Research Arm test, before and 4 weeks after treatment with botulinum toxin type-A
Total ARAT scores for all participants (n=14) before and 4 weeks after treatment with botulinum toxin. Minimum total ARAT score= 0, maximum total ARAT score= 57

Table 2.7

Action Research Arm Test data (ARAT): before and 4 weeks after treatment with botulinum toxin type-A.

ARATa: , ARAT subtest "Grasp", ARATb: subtest "Grip", ARATc: subtest "Pinch", ARATd: subtest "Gross Movement". Minimum ARAT score: 0, maximum ARAT score: 57. Grey cells indicate cases where treatment effects on the ARAT Total score were absent or negative.

Participant ID	ARATa before	ARATb before	ARATc before	ARATd before	ARAT total Before	ARATa after	ARATb after	ARATc after	ARATd after	ARAT total After	*Change ARAT total: After - Before*
A6	0	0	0	3	**3**	0	0	0	3	**3**	***0***
A5	0	0	0	3	**3**	0	0	0	3	**3**	***0***
A3	0	0	0	3	**3**	1	1	4	3	**9**	***6***
A7	1	3	2	5	**11**	2	3	6	5	**16**	***5***
C2	0	0	0	3	**3**	0	0	0	3	**3**	***0***
C1	0	0	0	3	**3**	1	0	0	3	**4**	***1***
C6	2	0	0	4	**6**	3	0	0	4	**7**	***1***
C0	3	0	0	3	**6**	2	0	0	4	**6**	***0***
B5	0	0	0	3	**3**	0	0	0	3	**3**	***0***
B7	0	0	0	3	**3**	0	0	0	3	**3**	***0***
B8	0	0	0	4	**4**	1	0	0	4	**5**	***1***
C5	0	0	0	0	**0**	0	0	0	3	**3**	***3***
B9	0	0	0	4	**4**	0	0	0	4	**4**	***0***
C3	0	0	0	4	**4**	0	0	0	3	**3**	***-1***
Median	**0**	**0**	**0**	**3**	**3**	**0**	**0**	**0**	**3**	**3.5**	***0***
iqr	**2.5**	**0**	**0**	**1**	**1.5**	**1.25**	**0**	**0**	**1**	**3.25**	***1.5***
Min	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**3**	***-1***
Max	**3**	**3**	**2**	**5**	**11**	**3**	**3**	**6**	**5**	**16**	***6***

2.4.4.4 Effects on Participant Satisfaction

Satisfaction data, taken at Week 4 following BTX-A, are presented in Table 2.8. On the 7-point scale, the median change and the most frequently occurring response was a "+2". Two of the 14 participants (A3, A5) felt that treatment had rendered their condition "a lot better", although one participant (C3) indicated it had got "a lot worse". When they were asked about any adverse reactions, none of the participants reported any.

Table 2.8
Participant satisfaction at 4 weeks after treatment with botulinum toxin type-A
Grey cells indicate cases where treatment effects were absent or negative.

Participant ID	Participant satisfaction
A6	2
A5	3
A3	3
A7	2
C2	1
C1	2
C6	1
C0	1
B5	1
B7	1
B8	2
C5	2
B9	2
C3	-3
Median	**+2**
iqr	**1**
Min	**-3**
Max	**3**

2.4.4.5 Summary of the effects of botulinum toxin type-A

In summary, Table 2.9 shows that botulinum toxin type-A, injected into UL muscles including the elbow flexors of stroke patients with chronic upper limb spasticity, resulted in a significant reduction of resistance to passive elbow extension, when assessed with the MAS. In contrast however, no significant changes were found in resistance to passive elbow extension, when this was measured with a biomechanical device, nor in the elbow flexor EMG - although there was a reduction following the intervention, but this did not reach statistical significance. BTX-A also resulted in a statistically significant improvement in arm function, evaluated with the ARAT. All except one participant reported that BTX-A had improved their condition and no adverse reactions were reported.

Table 2.9
Summary of results before and 4 weeks after treatment with botulinum toxin type-A
BTX-A: botulinum toxin type-A. MAS: Modified Ashworth Scale for passive elbow extension. $RTPM_{slow}$: Resistance to slow passive elbow extension, $RTPM_{fast}$: Resistance to fast passive elbow extension, EMG_{slow}: elbow flexor EMG during slow passive elbow extension, EMG_{fast}: elbow flexor EMG during fast passive elbow extension. ARAT: total Action Research Arm Test score.
MAS score "1+" was converted to "1.5" for the purpose of the analysis. For the MAS, the range instead of the iqr was calculated.

Dependent Variable	Before	After	Significance
MAS Median (range)	**2** (1.5 – 3)	**1.75** (1 – 3)	*
$RTPM_{fast}$ (N/deg) Mean (SD)	**0.45** (0.33)	**0.48** (0.37)	ns
$RTPM_{fast}$ – $RTPM_{slow}$ (N/deg) Mean (SD)	**0.12** (0.30)	**0.06** (0.25)	ns
Elbow flexor EMG_{fast} (μV) Mean (SD)	**3.71** (1.6)	**3.03** (0.78)	ns
EMG_{fast} – EMG_{slow} (μV) Mean (SD)	**0.77** (0.83	**0.41** (0.39)	ns
ARAT median (iqr)	**3** (1.5)	**3.5** (3.25)	*

Ns; non-significant, *: $p<0.05$.

In addition to the cohort data, changes in the outcome measures were examined for each of the participants (Table 2.10). To enable easier interpretation of the data, changes are noted only in terms of the direction (but not the magnitude) of change. The data show that only in two cases (A7 and B8), treatment effects were favourable across all outcome measures, whereas in all other cases the effects were mixed.

Table 2.10
Overview of the direction of change in each of the outcome measures for each subject: before and 4 weeks after treatment with botulinum toxin type-A
MAS: Modified Ashworth score for passive elbow extension, $RTPM_{fast}$ (N/deg): resistance to passive elbow extension during the MAS, EMG_{fast} (μV): elbow flexor EMG during the MAS, ARAT: Action Research Arm Test total score. Mv: Missing value.
Grey cells indicate cases where treatment effects were absent or negative.

Participant ID	MAS	$RTPM_{fast}$ (N/deg)	EMG_{fast} (μV)	ARAT	Participant satisfaction
A6	0	-	-	0	+
A5	-	-	+	0	+
A3	0	-	-	+	+
A7	-	-	-	+	+
C2	-	+	+	0	+
C1	0	+	-	+	+
C6	0	+	-	+	+
C0	-	+	+	0	+
B5	0	+	-	0	+
B7	0	Mv	Mv	0	+
B8	-	-	-	+	+
C5	-	+	-	+	+
B9	0	+	-	0	+
C3	0	-	+	-	-

2.4.5 SUMMARY

The conclusions from the results, and their implications for the null hypotheses, formulated in section 2.2, are listed in Box 2.6.

Box 2.6
Study hypotheses: conclusions

BTX-A: botulinum toxin type-A. MAS: Modified Ashworth Scale for passive elbow extension. $RTPM_{slow}$: Resistance to slow passive elbow extension, $RTPM_{fast}$: Resistance to fast passive elbow extension, EMG_{slow}: elbow flexor EMG during slow passive elbow extension, EMG_{fast}: elbow flexor EMG during fast passive elbow extension. ARAT: total Action Research Arm Test score.

H_0A: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference MAS.	**Reject**
H_0B1: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference in $RTPM_{fast}$	Accept
H_0B2: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference in $RTPM_{fast}$ minus $RTPM_{slow}$	Accept
H_0C1: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference in EMG_{fast}.	Accept
H_0C2: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference in EMG_{fast} minus EMG_{slow}	Accept
H_0D: Comparing baseline with 4 weeks after BTX-A, there will be no significant difference in total ARAT score.	**Reject**

2.5 DISCUSSION

2.5.1 INTRODUCTION

The findings presented above will now be discussed, according to order in which the aims were set out (section 2.2) and compared with similar published work. This is followed by a discussion of the limitations and sources of error of the study and their possible implications for the results. Finally, ideas for further research and clinical practice involving BTX-A will be presented.

2.5.2 EFFECTS OF BOTULINUM TOXIN TYPE-A

Modified Ashworth Scale

BTX-A resulted in a statistically significant reduction (p=0.02) in the MAS for passive elbow extension, although the median change was 0 points. A reduction of 1 point on the Ashworth Scale is considered to be clinically significant (Albright *et al.,* 1993, cited in Simpson *et al.,* 1996), which was the case for only two of the 14 participants (B8 and C5, Table 2.5). For four participants, the reduction was less than 1 point, with scores changing from a "1+" to a "1" or from a "2" to a "1+" (Table 3.6)[10]. Finally, the MAS did not change in the remaining eight participants.

In conclusion, although the improvement in the MAS was statistically significant for the group, it would be considered as clinically significant in only two of the 14 participants. The magnitude of these effects appears to be smaller than those generally reported in the literature (Bakheit *et al.,* 2000, 2001; Bhakta *et al.,* 2000; Brashear *et al.,* 2002; Childers *et al.,* 2004; Hesse *et al.,* 1998; Simpson *et al.,* 1996). Before concluding that the effects of BTX-A on resistance to passive movement are limited, the properties of the MAS need to be considered first. Any subtle change following treatment may not have been of sufficient magnitude to be expressed as a change in score, which highlights the limited sensitivity of the MAS. Additionally, given the fact that the MAS at baseline was "1+" for the majority of participants, a ceiling effect should also be considered; as it would have been unlikely for participants with chronic spasticity to reach a score of "0" on the MAS following one intervention. In fact, the level of spasticity in the studies by Bakheit *et al.* (2000, 2001), Bhakta *et al.* (2000), Brashear *et al.* (2002), Childers *et al.* (2004), Hesse *et al.* (1998) and Simpson *et al.* (1996) was more severe, as judged from their eligibility criteria (Appendix 1.4), and therefore there would have been more room for improvement compared to the present study.

$RTPM_{fast}$

At baseline, mean $RTPM_{fast}$ during the MAS was 0.45 N/deg (SD 0.33). This value was comparable to that reported in previous work with a similar group of participants

[10] The scoring criteria for the MAS are described in section 2.3.3.2.

and the same measurement system (Pandyan *et al.*, 2001). There were no other comparable data in the literature.

Interestingly, in contrast to the findings on the MAS, BTX-A did not have any significant effect on $RTPM_{fast}$ in this study. This could constitute a clear example of experimenter bias, since there was no control group and the assessor was not blinded in this pilot study. Since the assessor had no influence over the registration of the RTPM data – in contrast to the MAS data - the biomechanical data were devoid of this source of bias.

The effect of BTX-A on the velocity-dependency of RTPM was also non-significant. In fact, mean $RTPM_{fast}$ increased – albeit marginally - from 0.45 N/deg (SD 0.33) at baseline to 0.48 N/deg (SD 0.37) four weeks after treatment, but this difference was not significant. Although $RTPM_{fast}$ decreased in six participants following BTX-A, it increased in seven (table 2.6). The reason for this is unclear, considering that in five of the participants in whom RTPM increased, elbow flexor EMG actually decreased.

Before making any conclusions, it is important to consider one potentially confounding variable: the average speed at which the elbow was extended was higher at Week 4 than at baseline (table 2.4). This could have led to an increase in EMG, which in turn could have led to an increase in RTPM. However, this difference was not significant and in actual fact, mean elbow flexor EMG was lower at Week 4 than at baseline. Therefore, the non-significant increase in RTPM following BTX-A must have been caused by biomechanical factors. As indicated before, table 2.2 shows that the majority of participants had contractures of their elbow joint and these soft-tissue changes may have masked any impact which BTX-A may have had on the neurogenic contribution to RTPM.

In conclusion, this pilot study suggests that BTX-A administered to the elbow flexors did not reduce RTPM encountered during passive elbow extension in a sample of people in the chronic stage after stroke, many of whom presented with elbow flexor contractures.

EMG_{fast}

BTX-A decreased mean elbow flexor EMG_{fast} from 3.71 μV (SD 1.6) to 3.03 μV (SD 0.78, table 2.6), but this reduction was not statistically significant. A decrease in activity in muscles injected with BTX-A was expected, as this is the primary action of the drug (Sheean 1998b, Davis and Barnes, 2001). The fact that this reduction was

not statistically significant may be explained by the small sample size together with the considerable variability in elbow flexor activity, especially at baseline (table 2.6). Some of the variation may be attributable to methodological inconsistencies, such as differences in electrode placement. These issues will be further discussed in section 2.5.3. Another factor may be the variation in BTX-A dosage, which will also be discussed in section 2.5.3. Interestingly, a velocity-dependent response in EMG output was registered, with a brisk stretch resulting in significantly higher EMG output than a slow stretch, both at baseline and four weeks after treatment. However, this sensitivity did not change significantly following BTX-A, suggesting that the expression of the actual phenomenon of spasticity, as defined by Lance (1980) was merely diminished but not removed by the toxin.

It is not possible to directly compare the data from this study with any other work, but the findings seem to concur with those from two other studies. Miscio *et al.* (2004) found a reduction in stretch reflex excitability (expressed as the stretch reflex area and stretch reflex threshold speed) of the wrist flexors following BTX-A, although data reporting was patchy. In addition, Girlanda *et al.* (1997) and Miscio *et al.* (2004) measured the M-wave and H-reflex and both reported a reduction in H_{max} as well as M_{max}, whilst the H_{max}/M_{max} ratio remained unchanged, which suggested a damping of the peripheral expression of the stretch reflex only. The finding that, in this study, the change in EMG was not significant may be explained by the differences in dependent variables; EMG, as calculated in the present study, reflected the overall power of the response, whereas parameters pertaining to the stretch reflex may have been more responsive to change.

ARAT

Given the fact that the total ARAT scores ranged from 0 ("can perform no part of the test") to 57 ("performs test normally"), it is apparent from table 2.7 that arm function in the study population was severely impaired.

Four weeks after BTX-A, arm function showed a statistically significant improvement, with the median total ARAT score changing from 3 (iqr 1.5) to 3.5 (iqr 3.25). Six of the 14 participants improved, with the most frequent increase being 1 point on the ARAT (n=3) and the greatest increase being 6 points (n=1) (table 2.7).

However, the performance of seven participants did not change whilst one participant lost 1 point.

Altogether, the magnitude of the change was marginal, as it did not reach the Minimal Clinical Important Difference (MCID), set at 10% of the range of the scale, i.e. at 5.7 points (van der Lee *et al.,* 1999). This was only attained by one participant (A3) and approached by one other (A7, table 2.7). However, the magnitude of the MCID for the ARAT does not appear to be based on a clinical rationale. As already stated, participants' arm function in this study was severely limited and one could argue that an increase of 6 points would be unrealistic.

It is difficult to compare this finding with the literature; as indicated in the review, only one RCT addressed arm function with a published scale (Bakheit *et al.,* 2000), which did not demonstrate an effect, but the scale used in that study (i.e. the RMA/UL) was less sensitive . In conclusion, in line with van Kuijk *et al.* (2002), it is clear that further RCTs are required to investigate the effects of BTX-A on arm function.

Participant satisfaction

The data related to participant satisfaction (table 2.8) show that all participants, except one, were satisfied with the intervention, yielding a median improvement of 2 points (iqr 1). Given that only two outcome measures (i.e. the MAS and the ARAT) yielded results that were statistically significant (although their clinical significance was questionable), the origin of this enthusiasm was not entirely clear. With regards to the participant who was not satisfied with the treatment, the outcomes were unremarkable, except in terms of arm function, as this was the only participant who deteriorated (albeit by one point only).

One explanation for the discrepancy between satisfaction scores and the more objective results is that this study only included selected outcome measures. It is therefore entirely plausible that participants may have experienced other effects which were not included in the assessment battery. Participants in the study by Panizza *et al.* (2000) commented on experiencing greater freedom and a sensation of reduced tightness, which were not addressed in the present study. Other authors described effects of BTX-A on care (e.g. Bakheit *et al.,* 2000, 2001; Bhakta *et al.,* 1996, 2000; Hesse *et al.,* 1998), the burden of care and pain (e.g. Bhakta *et al.,* 1996; Sampaio *et al.,* 1997) – variables which may be especially relevant to those

with severe levels of UL impairment. Future investigations would need to explore which outcomes are considered to be most relevant by the service users and select outcome measure(s) accordingly.

Alternatively, it is plausible that the high levels of satisfaction could – at least partially - be attributed to a placebo effect. Injections, after all, are potentially powerful placebos, as the studies by Bakheit *et al.* (2001), Brashear *et al.* (2002) and Childers *et al.* (2004) showed. These findings further highlight the need for properly controlled studies.

Although it was reassuring to find that most participants felt that treatment had improved their condition, the VAS used in this study did not provide any information about which outcomes had changed. It is perfectly possible that participants had very different expectations with regards to treatment outcomes compared with clinic staff or the research team. In order to be able to identify which goals participants wish to achieve through BTX-A treatment, future studies need to include a more detailed, patient-centred outcome measure, as suggested by Bhakta *et al.* (1996). However, it is important that these be properly validated.

In summary, the data from this pre-experimental study indicate that, four weeks following an injection of BTX-A into upper limb muscles of people with chronic spasticity after stroke, there was a trend that elbow flexor activity had decreased, but this was not statistically significant. BTX-A did not appear to reduce the velocity-dependency of spasticity. Resistance to passive elbow extension was also significantly decreased when assessed with the MAS, but this was not the case when this was quantified using a biomechanical device. As the former measure was subject to experimenter bias whereas the latter was not, it was concluded that BTX-A did not have an effect on RTPM. BTX-A resulted in a statistically significant improvement in arm function, although the clinical significance of this improvement was marginal in most participants.

2.5.3 LIMITATIONS AND SOURCES OF ERROR

Design

Absence of control group

The absence of a control group in this exploratory study was probably its most important shortcoming. Because experimenter bias could not be excluded, a calculation of the effect size was omitted. In the light of this methodological limitation, the results pertaining to the effects of BTX-A need to be interpreted with caution. As mentioned before, Bakheit *et al.* (2000), Brashear *et al.* (2002) and Childers *et al.* (2004) found sizable placebo effects in their RCTs.

The main reason for not including a control group in the present study was that its nature was primarily exploratory, the aims being primarily to pilot a measurement system and – but only as a secondary aim – to explore the effects of BTX-A. Having completed this pilot study, the methodology could then be employed in properly controlled trials to further investigate the effects of BTX-A.

Single baseline

The study was limited by the fact that there was a single baseline assessment only, hence confidence about the stability of the participant's status was limited. In the literature review, only one study (Bhakta *et al.,* 2000) used a double baseline, separated by one week. However, the current study involved stroke patients who were at least 12 months post stroke and therefore their status was not expected to change considerably, although this was not formally established. The drawback of including a multiple baseline in this study would have been the extra travel required; with the clinical centre covering a large geographical area, this would have been prohibitive for many participants. Where practicable however, future studies may be improved by including a double baseline assessment.

Limited follow-up time

Treatment effects, which usually last around three months (Sheean 1998c), were only followed over the first four weeks. This point had been chosen because other work suggested that at this point the effects from BTX-A treatment are most pronounced (e.g. Simpson *et al.,* 1996) and this was sufficient to fulfil the aims of the

present study. However, in order to determine any longer-term effects, further studies would need to include a follow-up period of at least one full BTX-A cycle.

Study sample

The sample in this study was very small and heterogeneous with respect to type, severity and time since the stroke, whilst the impact on handedness also varied. Furthermore, as table 2.3 shows, there was substantial variation in BTX-A treatment, both in terms of injection sites and dosage; in the m. biceps brachii alone, the dosage varied between 25-300 MU (mean 71, SD 70) and various amounts of toxin were injected into other elbow flexors. Altogether, the total BTX-A dosage injected into elbow flexors varied between 100-500 MU., which may have contributed to differences in outcomes between participants (see Simpson *et al.*,1996 and Bakheit *et al.*, 2000). These two dose-ranging studies indicated that a larger dosage of botulinum toxin was likely to result in a greater reduction in the MAS. In future studies, BTX-A could either be standardised or, in a large enough sample, stratified according to BTX-A dosage and sites.

A small sample with a heterogeneous population presents a classic problem in neurological rehabilitation research and several authors have highlighted the need for larger samples with homogeneous populations to achieve sufficient power (see Kwakkel *et al.*, 1999a). Alternatively, heterogeneous groups may be stratified according to relevant characteristics, but the sample in this study was too small for this procedure.

At the time of this study, there were no comparable data in the literature on which a power calculation could be based and therefore, a convenience sample was selected. In order to improve the power of future investigations, either a multi-centre RCT or a more extensive single centre study will be required to replicate and corroborate the findings from the present study.

Speed of testing

As mentioned in section 1.2.4.2 and also highlighted previously, the spasticity measurement device used in this study was manual and therefore the speed at which the elbow was extended could not be standardised. Although this was a

considerable limitation of the instrument, this had been a conscious design decision in order to avoid problems with health, safety and practical feasibility, commonly associated with the controlled displacement or controlled torque devices reviewed in section 1.2. However, since spasticity is a velocity-dependent phenomenon, variation in speed may confound the data as follows: a higher speed will trigger a stronger stretch reflex response and the associated increase in EMG may result in a rise in RTPM. However, there is still debate in the literature as to the contribution of EMG to RTPM (Pandyan et al., 2005). Additionally, a higher speed may affect the visco-elastic properties of the soft tissues involved (described in section 1.2.1.4), which may in turn affect the biomechanical contribution to RTPM.
The presence of an electrogoniometer enabled speed to be calculated post hoc. However, a limitation of the method for calculating speed was that it only provided a crude average value; it did not yield any information on acceleration or deceleration, which might have affected the elbow flexor response and thus RTPM. As table 2.4 shows, there was a very considerable intra-as well as inter-participant variation in average speed, but the difference between the speed at baseline and re-assessment was not statistically significant.

Despite the lack of standardisation of the testing speed, comparable RTPM data were found in Pandyan *et al.* (2001), where the same device was used by a different examiner in a group with sub-acute stroke patients. The average speed of the first of three repeated measures was lower (i.e. 36.5 deg/s, SE 5), but that of the second and third were 61 deg/s (SE 5) and 64 deg/s (SE 6) respectively, which was comparable to 56 deg/s (SD 43) and 65 deg/s (SD 54) found in the present study. Clearly, the standard error of the mean speed in the study by Pandyan *et al.* (2001) was much lower than that in the present study. However, that study involved sub-acute patients (i.e. one week after stroke) and it is unlikely that they would have developed the severity and variation of biomechanical changes, observed in the present study.
In a study of RTPM in a group of non-impaired university students, a mean RTPM of 0.0055 N/deg (SD 0.003) was documented (Barnaby, 2002 and Barnaby *et al.* 2002), indicating not only a very low RTPM, but also a very high reliability. The differences in variation of RTPM between this study and those involving stroke patients may be explained partially by inter-rater variability, but also by the

differences in study population: all participants in Barnaby's study were young and unimpaired and thus would not have any of the biomechanical and neurogenic factors that contribute to RTPM and its variability.

Some researchers have used a metronome to control the timing of passive movement (e.g. Marchese *et al.*, 2001, see section 1.2.4.2). This method would probably be effective in cases where RTPM is predictable, but this is unlikely to be the case with the more severely affected patients. In most cases, and particularly where a "catch" is encountered, a change in RTPM could set in at any point in time. This event would alter the speed at which the limb is moved, which in turn would change the time required to cover the range of movement, at which point the synchronisation with the metronome would be lost. However, it may be possible, once an individual patient has been tested, to set a metronome to a frequency specific to that joint for that patient (Pandyan, personal communication, 28/09/04). By doing so, intra-participant variation may be reduced, but inter-participant variation would remain unresolved.

The considerable variation in testing speed highlights the need for further work to investigate intra- as well as inter-rater reliability when using the DATA system. The test procedure needs to be practised, as it varies from the traditional MAS by having to manipulate the handle of the device instead of the participant's arm. In recognition of this requirement, a total of 11 participants had been involved in the pre-pilot phase of this study. However, whether the technique had undergone any change over the duration of the study was not documented. Any alterations in testing speed would have confounded the results, with an increase in speed resulting in an increase in EMG response, which in turn may also have increased RTPM.

Outcome assessment tools

Modified Ashworth Scale

The MAS is well known for its problems, and the critique voiced by Pandyan *et al.* on this tool (1999, 2002, 2003) were partially based on the results from this study. The only – albeit debatable - advantage of using the MAS is that it enables findings to be compared with similar studies. However, if one of the tests must be used, the

original Ashworth Score would appear to be less problematic than the MAS (Pandyan *et al.,* 1999).

Resistance to passive movement ($RTPM_{fast}$)

A limitation of the DATA system was that it measured force, but did not control for moment arm. Measuring torque instead of force would have been preferable, as this would have avoided the effects of differences in moment arm on the output and enabled more accurate comparisons to be made, both within the same participant and between different participants.

Although a standardised position was used for testing the MAS, many participants had limited ROM in their shoulder and/ or elbow. Since it was imperative to remain well within each participant's pain-free ROM during testing, some variation, mostly with regard to the degree of shoulder abduction and elbow extension, was inevitable. Being aware that participants might have contractures and/ or pain at end ROM may also have led the assessor to be more cautious, e.g. by reducing the speed of testing, which might have affected the spasticity response. In addition, participants with pain may, unintentionally, have protected their joint by increasing the level of activity of the muscles being stretched. These variations in testing methodology may all have altered the response.

Some errors may also have occurred during the application of the device, which was strapped onto the participant's arm using Velcro, with one end block of the electrogoniometer being taped onto the upper arm. Although care was taken to place the instrument consistently, some variation would have been inevitable due to anthropometrical differences between participants and variation within each participant between baseline and re-assessment. Care was taken to firmly strap the instrument onto the participant's arm, but some slippage may have occurred during testing, which may have resulted in some artefacts in the force and angle data. The electrogoniometer was particularly prone to skin movement, especially in participants with marked atrophy of the mm. Biceps and Triceps brachii.

A limitation of the methodology used in this study was that RTPM may have changed around joints other than the elbow, e.g. the wrist or fingers. However, this

possibility was not explored, primarily because the DATA system had only been designed for the elbow joint at the time. Hence, the omission of recording changes in RTPM over other joints was a limitation of the study.

With regards to the goodness of fit of the data to the linear regression line, table 2.6 shows that r^2 varied between 0.29 and 0.99 before BTX-A and between 0.50 and 0.99 after BTX-A. In total, only two curves (from the same participant) had an r^2 of less than 0.6, which suggests that the majority of shapes could be considered to be linear (Pandyan *et al.,* 2001).

RTPM had been calculated over the full PROM of the elbow joint. However, upon inspection of the data, it appeared in some cases that there were artifacts at the start or end of range of movement. These could be explained by inertial effects at times when acceleration or deceleration was high. Similar observations had also been noted by Lai *et al.* (1996). Therefore, in future studies featuring this instrument, the ROM over which RTPM and EMG were calculated should be restricted in order to avoid these artifacts.

Elbow flexor EMG (EMG_{fast})

Unsurprisingly, some participants found it difficult to relax during testing - especially during the first assessment. Some participants may have contracted their muscles unintentionally during testing, which may have increased the amplitudes of the short- and long latency reflexes (i.e. M1, M2 and M3) of the muscles involved (Toft *et al.,* 1989), which would have elevated the EMG output.

As indicated earlier, repeated testing was necessary in some cases -albeit no more than three trials per session. This may have reduced RTPM as well as EMG, due to its influence on thixotropy (Hill, 1986 as cited in Walsh, 1992) as well as the stretch reflex (Cathers et al., 1996). An inevitable source of error during this procedure was the assessor's judgement of the validity of the trial (e.g. whether the muscle groups were relaxed, or whether the participant had followed instructions). A flow diagram, detailing the various decisions and the criteria involved in these, would be required to render this methodology more reproducible in future, both within a single assessor, as well as between different assessors.

Additional problems, commonly associated with the application of EMG that may have confounded the results in this study included: 1) inherent instability of the signal (predominantly in the 0-20 Hz domain), 2) motion artefacts due to movement of the electrodes relative to the muscle group being tested and movement of the leads, 3) within- and between-subject differences in electrode placement and 4) ambient noise in the testing room due to the power line and electronics (De Luca, 1997). In order to reduce the first source of error, a bandwidth filter of 20-450 Hz had been used (as per standard with the Delsys system), which is designed to remove this source of noise. With regards to motion artefacts, sensors and the differential electrode had been taped firmly onto the skin by means of medical tape. In some cases however, placement of the electrodes suffered from skin movement with respect to the muscle; i.e. electrodes were displaced medially when the arm was brought into abduction, especially in those with atrophy of the upper arm muscles. This problem may have affected the data, as the electrode was no longer placed in its optimal position to detect the EMG signal. Noise due to movement of the leads was reduced by taping them onto the participant's skin, while allowing movement to take place. However, with the MAS being a dynamic test, some movement of the leads was inevitable. Regarding the third point, the EMG electrodes were placed on the basis of visual inspection and palpation. This procedure is inevitably subject to error and hence electrode placement may have varied both within and between participants. The fourth factor was ambient noise from the power line and electrical equipment in the testing room. This was filtered out by means of a notch filter. Although this method is effective in terms of filtering out this particular source of noise, it has also been criticised, as in practice it may additionally remove part of the dominant energy of the EMG spectrum (which typically ranges from 50-100 Hz., De Luca, 2002).

Action Research Arm Test

In this study, where arm function was generally severely impaired, the main limitations of the ARAT were its floor effect, coupled with limited sensitivity. Many participants could not perform any of the tasks except the gross movement items (table 2.7). Hence, the most frequently occurring change in item score was from 0 to 1 (i.e. from "can perform no part of the test" to "performs test partially "). However, participants may have improved with respect to the extent to which they

could complete a task, but if they remained unable to perform the task in its entirety, they would not be given a higher score. Additionally, in a sample such as in the present study, one would not normally expect item scores to improve from 2 to 3 (i.e. from "completes test but takes abnormally long time or has great difficulty" to "performs test normally"). Altogether, these conditions further reduced the – already limited - scope to note any changes in performance on the ARAT.
The most ambiguous score of the ARAT is perhaps the "2", as the criteria "great difficulty" and "abnormally long time" are open to debate as well as experimenter bias, which the current design was susceptible to. Hence, occasionally, a score of "3" may have been awarded instead of a "2" and vice versa, although this would not have occurred very often, as very few participants were able to perform at this level.

Additionally, one important shortcoming of the ARAT is that it documents mainly *what* has been achieved, but not *how* this was achieved, i.e. the kinematics of the activity are omitted. As such, the ARAT is a descriptive tool with limited specificity, while its explanatory value is minimal.
Taken together, in order to reduce the floor effect of the ARAT, improve its sensitivity, reliability and specificity, future studies could integrate the ARAT with motion analysis technology, e.g. electrogoniometry of the elbow and/ or wrist or, more comprehensively, full 3D motion analysis.

Participant satisfaction

The tool used to assess satisfaction in this particular study had not been validated and therefore, the data need to be interpreted with caution.
Quite separate from the psychometric properties of this scale, it is possible that some participants may have aimed to please the research team who recorded the responses. An independent assessor would have circumvented this issue, but this was not feasible at the time. Additionally, participants may also have wished to confirm their own (unconscious) belief that the treatment was worthwhile.
Taken together, the participant satisfaction tool in this study was useful for exploring the overall opinion on the BTX-A intervention, but it did not yield any further information. As indicated before, a patient-centred, yet validated outcome measure would be recommended for future work.

Other effects not assessed

The focus of this study was on spasticity, defined according to Lance (1980), which was measured as EMG of one muscle group (i.e. the elbow flexors). As explained in section 1.2, Lance's definition is highly specific and limited in scope. In the light of the proposed definition[11], it is conceivable that BTX-A may have affected other aspects of spasticity, e.g. co-contractions, associated reactions, spasms, which were not evaluated in this study. Future investigations could broaden their assessment battery to include some of these aspects, depending on their relevance.

2.5.4 IMPLICATIONS FOR RESEARCH AND CLINICAL PRACTICE

A number of suggestions for future investigations have already been made in the previous sections and these will not be repeated here.

With regards to the DATA system, it was found that - compared to the high level of accuracy and precision of the strain gauge and electrogoniometer *per se*, tested under laboratory conditions (table 2.1) - the outcome measures obtained in the actual test condition were less robust, which was associated primarily with the lack of standardisation of the testing speed. This finding highlighted the need for further research into intra- as well as inter-rater reliability with regards to the DATA system. Given the problems with repeated testing in human participants, which may reduce thixotropy (Hill, 1986 as cited by Walsh, 1992) and modify the stretch reflex response (Cathers *et al.*,1996), in addition to the volatility of spasticity *per se*, carrying out reliability studies on human participants with spasticity it is not straightforward. A possible solution for this problem could be a robotic arm, designed to enable specific biomechanical and neurogenic factors contributing to RTPM to be simulated. At the time of writing, however, it was important to note that the output from the DATA system was subject to a number of confounding variables – notably the variation in testing speed and that further reliability work will be required.

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[11] *"Disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles"* (Pandyan *et al.*, 2005: p. 5).

One noteworthy observation was that 14 of the total number of 25 participants (i.e. 56%) involved in the initial pilot work and the actual study did *not* receive any other form of physiotherapy or occupational therapy alongside BTX-A. This does not comply with the clinical guidelines on BTX-A treatment (Barnes *et al.,* 2001, Royal College of Physicians, 2002), which stipulate that BTX-A should be part of a comprehensive treatment programme. According to the Medical Director of the centre where the study took place (Barnes, personal communication 2004), the lack of service provision was due primarily to limited resources in community clinics and nursing homes. Participants themselves appeared to be highly motivated to engage in therapy; many of them asked what action they could undertake to support the effects of BTX-A.

It would be reasonable to assume that by not having had access to additional intervention, the potential of BTX-A might not have been realised fully. In this study, it was not possible to determine whether additional therapy had any impact. Interestingly, Table 2.7 shows that three of the participants, who did not receive additional therapy (A3, A7 and B8) improved more on the ARAT than did the others. However, with activities at home not being controlled for, it is possible that some participants may have carried out their own exercises, which would have confounded the results. It is clear that further work is required to investigate systematically to what extent BTX-A is effective on its own and compare this with a combination of BTX-A together with an additional form of intervention.

2.6 CONCLUSIONS

The primary aim of this study was to pilot a new method for measuring spasticity involving the elbow joint. Despite the methodological challenges of the DATA system in the actual testing situation, highlighted in the previous sections, the strengths of this system were that it provided a safe and relatively simple method for assessing spasticity, suitable for use in a clinical setting. Compared with the controlled displacement and torque instruments, discussed in section 1.2, its advantages in terms of clinical feasibility were clear. Compared with the clinical MAS, the device additionally solved a number of problems associated with this scale: it enabled the neurogenic components of RTPM to be distinguished from the non-neurogenic components, added quantitative data to the clinical scores and

improved the resolution of the data. Importantly, it was demonstrated that the device was capable of registering the velocity-dependent nature of spasticity in terms of EMG, although RTPM appeared to lack sensitivity – at least in this study, where biomechanical factors such as contractures may have dominated RTPM. Therefore, it was recommended that EMG be a prerequisite to include in any form of spasticity evaluation. On balance, the DATA system was considered to be the outcome measurement of choice for assessing spasticity and RTPM in the feasibility RCT, which will be reported in the following chapters.

The secondary aim of this study was to explore the effects of BTX-A on spasticity, arm function and participant satisfaction. Because of the absence of a control group, the results need to be interpreted with due caution. The findings suggested that BTX-A, injected into UL muscles including the elbow flexors, resulted in a reduction of elbow flexor EMG during rapid passive elbow extension, although this difference fell short of reaching statistical significance. Treatment did not result in any significant changes in biomechanically measured resistance to passive elbow extension, which was in contrast to the statistically significant reduction in the MAS. The discrepancy between the biomechanical and clinical measures of RTPM was explained by the lack of robustness of the MAS. BTX-A also resulted in a statistically significant improvement of arm function, although the clinical significance for individual participants of this effect was marginal in most cases.

It was noted that many participants involved in this study did not receive additional treatment together with BTX-A, which suggested that the potential of BTX-A may not have been realised fully. A common opinion is that BTX-A provides a "window of opportunity" (e.g. Bhakta *et al.,* 1996), which could be utilised to improve other outcomes, such as increased range of movement and active function (e.g. Girlanda *et al.,* 1997). Therefore, in line with other authors (e.g. Sampaio *et al.,* 1997, Bakheit *et al.*, 2001, Page *et al.,* 2003), it was recommended that further work be undertaken to investigate whether combining BTX-A with additional therapy would be more effective than BTX-A alone in people with chronic UL spasticity after stroke.

This issue will be explored in Chapters Three to Five, which report a feasibility RCT where the differential effect of an evidence-based skill acquisition programme,

administered together with BTX-A, will be compared with a passive form of treatment, also combined with BTX-A.

CHAPTER THREE

SKILL ACQUISITION AND BOTULINUM TOXIN FOR CHRONIC UPPER LIMB SPASTICITY AFTER STROKE: A FEASIBILITY RCT - *METHODOLOGY*

3.1 INTRODUCTION

The primary aim of the randomised controlled feasibility RCT, which will be reported in the next three chapters, was to investigate whether there would be any differential effect from an additional functional skill acquisition programme, based on the literature discussed in Chapter One, administered following botulinum toxin type-A (BTX-A) in people with chronic upper limb spasticity after stroke.

In terms of outcome measures, all three domains of the ICF (2001) would be represented: impairments (i.e. spasticity, resistance to passive movement), activity limitations (i.e. arm function and grip force) and participation restrictions. To obtain a more comprehensive picture of any treatment effects, the opinion of the study participants on the goals they set out to achieve and to what extent they were achieved was also included.

Outcomes were compared at four different points, i.e. at baseline (Week 0), following the intervention programme (Week 4), midway through the BTX-A cycle (Week 7) and before re-assessment for BTX-A treatment (Week 13).

As argued in section 1.7, in order to enhance functional, long-term neuroplastic changes, the skill acquisition programme should comprise relevant tasks, identified together with the participant and set at a realistic level. Given the characteristics of the participants in the pilot study, reported in Chapter Two, the tasks should be feasible for those with minimal hand function and limited range of movement in the

upper limb, and who may not have used their affected arm for some time. These requirements ruled out Constraint Induced Therapy and Arm Ability Training. Bilateral Isokinematic Training would appear to be most useful in the cognitive stage of learning in order to convey the image of the task. Mental Practice could be included and interspersed with PP to enhance the problem solving process and to increase the effectiveness of rest periods that were required to avoid mechanical overload. Practice and feedback would need to be structured in such a way to assist the learner to obtain a clear image of the activity in the cognitive stage of learning, whilst providing an opportunity to engage in increasingly independent problem solving in the subsequent stages of learning, in order to enhance long term carry-over into ADL.

The Medical Research Council (MRC) Framework for complex interventions (Campbell et al., 2000), classifies this type of intervention as "complex", as it comprised a number of different components. The investigation into the efficacy of this intervention proceeded through the following stages: by exploring the relevant theoretical issues, Chapter One covered the pre-clinical stage. Phase I involved identifying the detailed processes involved in the intervention, which was undertaken through pilot work (Appendices 3.6, 3.9, 3.11). Phase II involved the testing of this intervention in a feasibility RCT, will be reported in Chapters Three to Five: the current chapter describes the study aims, hypotheses and methodology. Chapter Four will describe the results, which will be further discussed in Chapter Five.

3.2 AIMS AND HYPOTHESES

The aims of this study were to:

1. To explore the differential effects of an additional functional skill acquisition programme, provided following BTX-A, in terms of:
   - Upper limb function, assessed by means of:
     - a standard outcome measure (i.e. the Action Research Arm Test (ARAT), Lyle 1981)
     - a patient-centred outcome measure (i.e. the Canadian Occupational Performance Measure (COPM), Law *et al.,* 1998)

- Resistance to passive movement during passive elbow extension, assessed by means of:
  - the Ashworth Scale (AS, Ashworth, 1964)
  - Resistance to passive movement (RTPM), using the DATA system (Pandyan *et al.,* 2001, 2003)
- Spasticity, measured as elbow flexor EMG, using the DATA system,
- Grip force (GF), evaluated using a Jamar dynamometer,
- Specific items from the Stroke Impact Scale version 3, (Duncan *et al.,* 2003), which were deemed to be most relevant for this study, i.e. SIS-5 (ADL), SIS-7 (hand function) and SIS-8 (Participation). The SIS is a self-report measure.

The primary outcome measures were: ARAT, COPM and EMG. The rationale for each of these outcome measures will be discussed in section 3.5.2.

The null hypotheses for this study are listed in Box 3.1.
All statistical tests were two-tailed, with alpha set at 0.05.

Box 3.1
Study hypotheses

BTX-A: botulinum toxin type-A. RTPM: Resistance to passive elbow extension (N/deg). EMG: elbow flexor EMG (mV). AS: Ashworth Scale for passive elbow extension. ARAT: total ARAT score. COPM-P: Canadian Occupational Performance Measure – Performance dimension, COPM-S: Canadian Occupational Performance Measure – Satisfaction dimension. The COPM was only assessed at baseline, week 4 and week 13 for reasons explained in section 3.5.2. SIS: Stroke Impact Scale. GF: grip force (N). EG: Experimental Group, CG: Control Group.

Null Hypotheses
$H_0$1: There will be no significant difference in change in Total ARAT score between EG and CG from baseline to week 4, 7 or 13.
$H_0$2: There will be no significant difference in change in COPM-P median score between EG and CG from baseline to week 4, 7 or 13.
$H_0$3: There will be no significant difference in change in COPM-S median score between EG and CG from baseline to week 4, 7 or 13.
$H_0$4: There will be no significant difference in change in EMG between EG and CG from baseline to week 4, 7 or 13.
$H_0$5: There will be no significant difference in change in RTPM between EG and CG from baseline to week 4, 7 or 13.
$H_0$6: There will be no significant difference in change in AS between EG and CG from baseline to week 4, 7 or 13.
$H_0$7: There will be no significant difference in change in GF between EG and CG from baseline to week 4, 7 or 13.
$H_0$8: There will be no significant difference in change in SIS- ADL between EG and CG from baseline to week 4, 7 or 13.
$H_0$9: There will be no significant difference in change in SIS- hand function between EG and CG from baseline to week 4, 7 or 13.
$H_0$10: There will be no significant difference in change in SIS- Participation between EG and CG from baseline to week 4, 7 or 13.

3.3 DESIGN

The design of this feasibility study was a randomised, placebo-controlled trial with two groups, four repeated measures and a blinded observer. Outcomes were assessed at baseline (Week 0), at the end of the 3-week intervention programme (Week 4), midway through the botulinum toxin type-A (BTX-A) cycle (Week 7) and at the end of one full BTX-A cycle (Week 13). Between-group differences in changes from baseline to week 4, baseline to week 7 and baseline to week 13 were compared. Fig. 3.1 provides an overview of the sequence of events during the trial, each of which will be described in detail in the following sections.

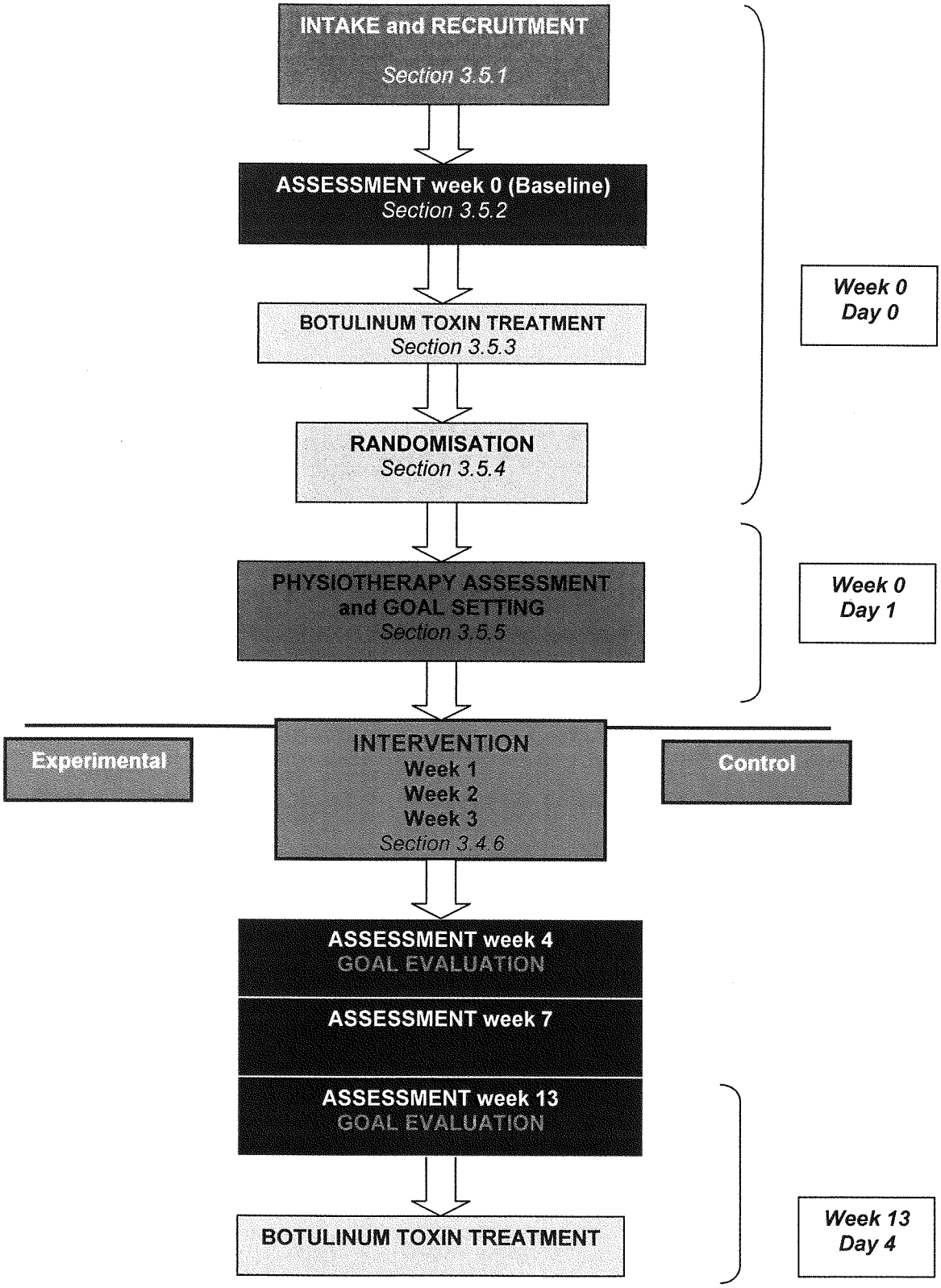


Figure 3.1
Flow diagram of all trial events, from recruitment to completion.
Assessment procedures for weeks 0, 4, 7 and 13 were identical – with the exception of the COPM, which was only assessed in weeks 0, 4 and 13.

3.4 STUDY SAMPLE

Participants for this study were recruited from the Outpatient Spasticity Clinic at Hunters Moor Regional Neurological Rehabilitation Centre (HM) in Newcastle upon Tyne, UK, a tertiary neurological rehabilitation centre, specialised in the management of spasticity. Patients were normally referred to HM through their GP, geriatrician or therapist for treatment with botulinum toxin-type A (BTX-A). The eligibility criteria are listed in Box 3.2.

Box 3.2
Inclusion criteria
BTX-A: Botulinum toxin type-A, UL: upper limb, ARAT: Action Research Arm Test, OT: Occupational Therapy, PT: Physiotherapy

Inclusion Criteria
Diagnosis Stroke as confirmed by CT/ MRI
Age between 20-80 years
Time after stroke ≥ 6 months
Receiving BTX-A for upper limb spasticity
BTX-A treatment for upper limb spasticity has been given on at least 1 previous occasion
UL function: some residual but not perfect function (i.e. score on subtest "Grasp" or "Grip" or "Pinch" of 1 ≤ ARAT≤ max.)
No other impairments of the movement system: any orthopaedic, rheumatological or other soft tissue impairments, which could affect upper limb function
No concurrent treatment (whether this be a single consultation or a structured programme) from a qualified OT/ PT for at least 6 weeks prior to BTX-A treatment
Speech comprehension: no more than mild deficit (i.e score ≤ 2 on item from Hemispheric Stroke Scale: patient has correctly followed 2 or 3 (out of 3) verbal commands)
No serious cognitive impairment (i.e. score ≥ 24 on Mini Mental State Examination)
Painfree passive range of movement of all upper limb joints as assessed with the Fugl-Meyer test
Informed consent obtained

An *a priori* sample size estimation was carried out to estimate the number of participants required for this study. There were no directly relevant data in the literature, since none of the published investigations had featured similar conditions and study population. The study most closely related to the current one was that by Page *et al.* (2001), investigating the effects of mental practice in a sample of people between 2 and 11 months after stroke (mean time: 6.5 months (SD 3.3)). Although the intervention for the control group (i.e. therapy only) was different from that in the current study, the mean difference in ARAT score between before and after the intervention was -0.7 points[1] (SD 2.0 points), indicating virtually no change. In contrast, the experimental group (i.e. therapy and mental practice) improved on average by 16.4 points (SD 15.1), which was well above the minimal clinically important difference (MCID) of 6 points for the ARAT (van der Lee *et al.*, 1999). According to Cohen (1988), these findings indicate a large effect size (i.e. > 0.8).

For the planned study to achieve 80% chance (power = 0.80) to detect an effect size of 0.9 with α set at 0.05, 21 participants would be required per group (Samuels, 1989). Allowing for 10% drop-out, the planned study thus required a total of 46 participants.

3.5 PROCEDURES

3.5.1 Recruitment

The procedures for intake and recruitment are outlined in Fig. 3.2. The steps that were undertaken in order to recruit participants are listed in Box 3.3.

[1] The paper reports that this difference is +0.7 points, but a recalculation using the raw data provided in the paper shows that this should be -0.7 points.

Box 3.3

Sequential steps in the recruitment process

1. The files of all patients, attending the Outpatient Spasticity Clinic were screened by the clinic nurse. If a patient appeared to match the eligibility criteria, staff would briefly inform them about the trial.
2. Those patients expressing an interest were contacted by the trial co-ordinator (fvw) by telephone, who explained the content and organisation of the study. Where possible, the patient's eligibility was briefly explored. If it was clear that the patient was not eligible (e.g. due to secondary pathology) or where the patient was not interested, no further action would be undertaken.
3. If potential participants agreed, they were sent further written information (Appendix 3.1: Trial Information). At least one week was allowed to consider the information, before they were contacted again by the trial co-ordinator, who addressed any questions which they or their carer(s) might have. Matters pertaining to eligibility were also further explained at this stage. If patients wished to take part, arrangements were made for recruitment at their next appointment at HM.
4. Upon their next appointment at HM, patients would firstly consult clinic staff regarding their BTX-A treatment. In cases where this was to be discontinued, they would no longer be eligible for the trial. If BTX-A treatment were to be continued, they would be considered for the study.
5. Patients and their carer(s) were then given an opportunity to discuss any remaining questions with the trial coordinator and if they wished to take part, their eligibility was formally checked (box 3.2). Since the experimental condition as well as the assessment procedures incorporated verbal instructions, patients with impairments of speech comprehension or cognition could not be recruited. Patients with other upper limb impairments that affected arm function could also not be accepted, in order to avoid confounding variables. Specifically, those with pain of their upper limb were not included in order to avoid potential exacerbation. To minimise possible carry-over effects from previous intervention, patients who had been consulted by a therapist up to six weeks previously (even if only a single consultation), could not take part. Patients should have received BTX-A on at least one previous occasion, in order to establish whether this was an appropriate form of intervention.
6. If patients matched the eligibility criteria and provided informed consent (Appendix 3.2), they were recruited into the study. Study participants would be assessed at baseline before returning to the clinic to receive their BTX-A treatment.

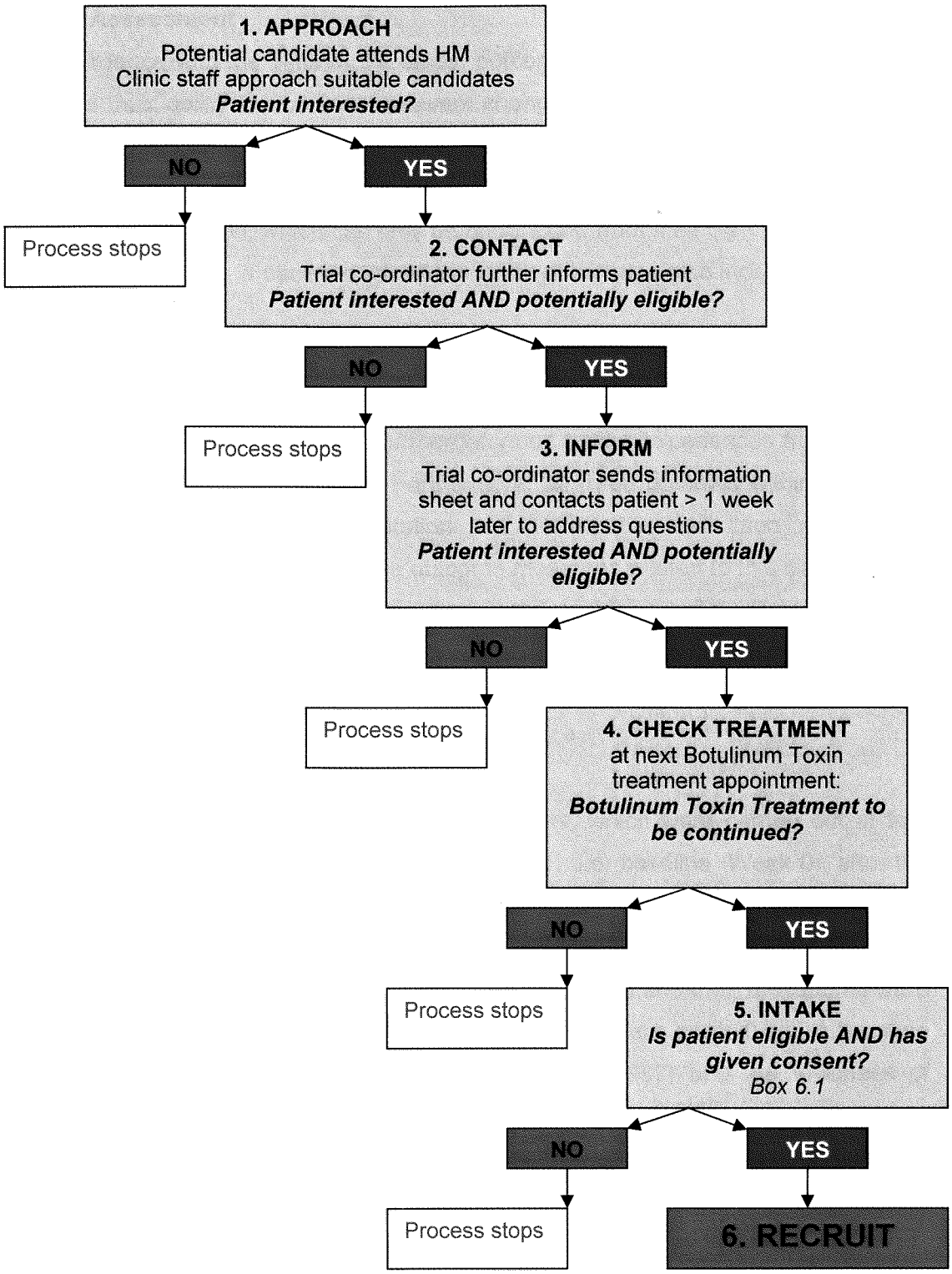


Figure 3.2
Flow diagram of recruitment procedure
HM: Outpatient Spasticity Clinic at Hunters Moor Regional Neurological Rehabilitation Centre

3.5.2 Assessment

In accordance with the aims of the study, outcome measures were selected on the basis of their ability to document relevant changes in upper limb impairments and activity limitations. Additionally, cognisance was given to the fact that the meaning of impairments and activity limitations is embedded in the personally constructed reality of each person, which can only be understood from their own perspective. In order to explore this, a patient-centred assessment tool was also included.

Further, the selection of the outcome measures for this study was based on the criteria of clinical relevance, scientific robustness, sensitivity to relevant change and feasibility (Wade, 1992) and was further informed by the experiences from the pilot study, reported in Chapter Two. Furthermore, all three domains within the WHO ICF, i.e. impairment, activity limitation and participation restriction were to be included. Fig. 3.3 indicates how the outcome measures related to this classification. It needs to be noted that a number of outcome measures include items related to more than one domain. The following section explains the rationale for choosing each outcome measure, in addition to the protocols for data collection. Actual assessment proformas are included in Appendix 3.4.

Figure 3.4 outlines the sequence of assessments, which were carried out at four points in time during the trial (outlined in Fig. 3.1), i.e. baseline (Week 0), after the three-week intervention (Week 4), at mid point in the BTX-A cycle (Week 7) and at the end of the BTX-A cycle, just prior to re-assessment at the Spasticity Clinic (Week 13). The order in which the tests were performed and their procedures were identical for each session, apart from two tests that were carried out at baseline only, namely the line bisection test (Adams *et al.*, 1987) and the Vividness of Movement Imagery Questionnaire (VMIQ, Isaac *et al.*, 1986). The line bisection test was carried out to assess the degree of neglect, while the VMIQ was used to gauge the participant's ability to generate visual images of movement. These two tests were included because the literature had indicated that neglect (van der Lee *et al.*, 1999; Feys *et al.*, 1998) as well as movement imagery ability (Doheny, 1993) were potential covariates.

All assessments were carried out by the same assessor (fvw), who was blinded with regard to the participants' treatment allocation. The exception to this was the physiotherapy-specific assessment (section 3.5.5), which was carried out by the research physiotherapist at baseline, as this information was required in order to administer the intervention.

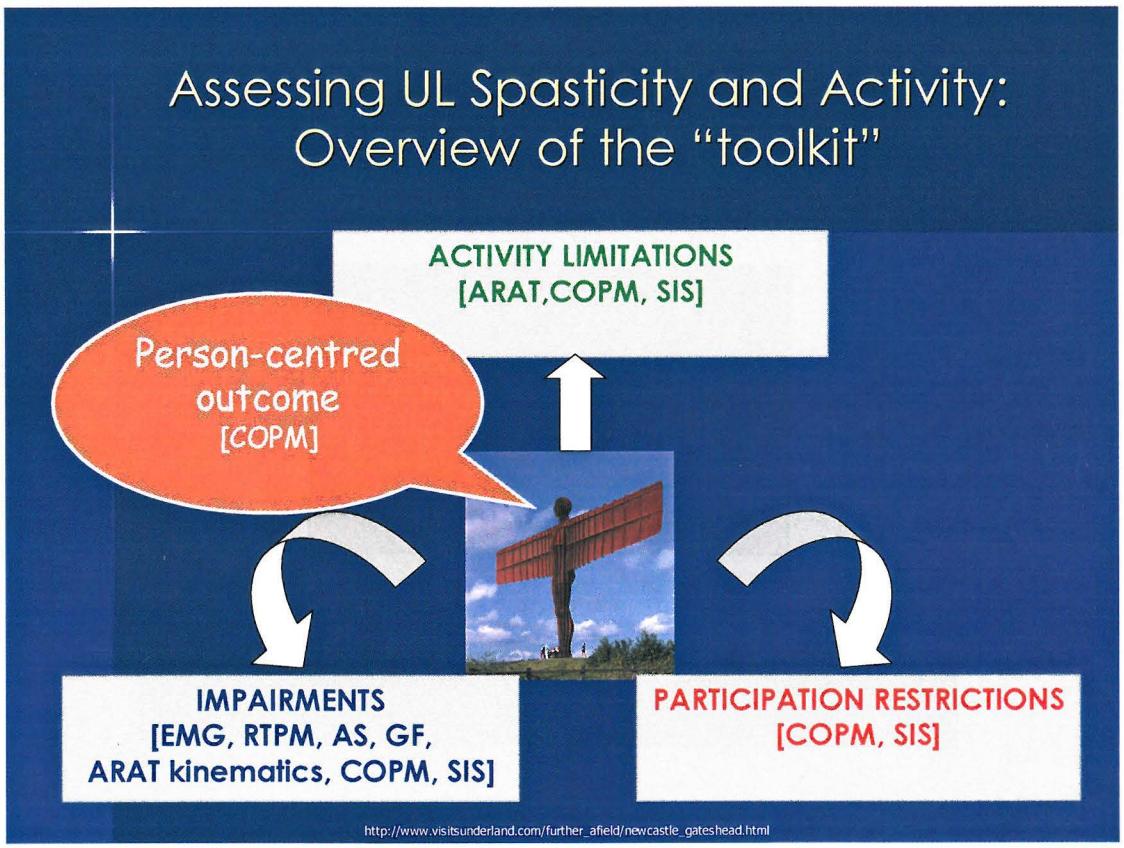


Figure 3.3
Overview of assessment tools for the study in the context of the ICF.
Outcome measures are categorised according to the WHO ICF classification. ARAT: Action Research Arm Test; COPM: Canadian Occupational Performance Measure; SIS: Stroke Impact Scale; EMG: elbow flexor EMG; RTPM: resistance to passive elbow extension; AS: Ashworth Scale; GF: grip force. Note that some outcome measures incorporate more than one level of analysis.

[Picture: http://www.visitsunderland.com/further_afield/newcastle_gateshead.html]

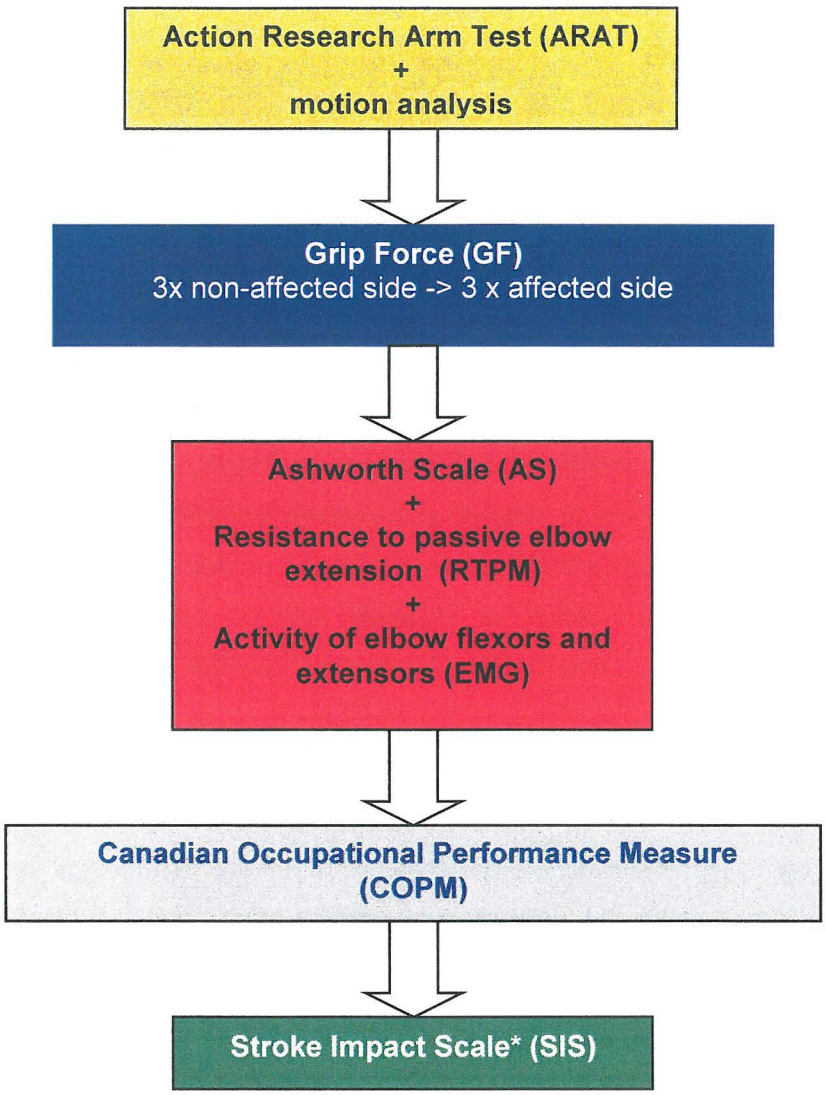


Figure 3.4
Flow diagram of assessment procedure
The order of testing was identical for each assessment point (i.e. weeks 0, 4, 7, 13), with the exception of the Canadian Occupational Performance Measure (COPM), which was carried out by the research physiotherapist at weeks 0, 4 and 13.
*The SIS was a questionnaire, which participants completed at home.

3.5.2.1 Action Research Arm Test

Rationale

The reasons for selecting the Action Research Arm Test (ARAT, Lyle, 1981) for this study were identical to those described for the pilot study in Chapter Two. Furthermore, with the focus of this study being on upper limb function, it was chosen as the primary outcome measure.

Protocol

The protocol was identical to that used in Chapter Two (section 2.3.3.2), which was fully described in Appendix 2.3 and Platz *et al.*, 2005). Since the start of this study, further evidence had emerged to suggest that the ARAT was more likely to be a unidimensional scale, thereby refuting the division of items into subtests (van der Lee *et al.*, 2002). In order to be able to compare the results from this study with previous work however, it was decided to adhere to the original version, supplemented by the guidelines formulated by Platz *et al.* (1999, 2005).

Three-dimensional reconstruction of upper limb kinematics using Vicon

Rationale

An important limitation of the ARAT is its limited sensitivity, which originates from its four-point ordinal level scale, which offers only a crude tool to categorise performance. In order to overcome this limitation and improve sensitivity, the ARAT was integrated with 3D motion analysis, using the Vicon system (Vicon 512 Oxford Metrics Ltd.). The Vicon system is an opto-electronic system that registers the 3D coordinates of reflective markers, placed on a participant, by means of infra-red cameras. In contrast to the ARAT, which primarily yields information about the extent to which a task is completed, Vicon data yield a full, quantitative 3D reconstruction of the kinematics of the performance on the ARAT.

Unfortunately however, due to resource constraints that only emerged during the course of the study, the full 3D analysis of upper limb kinematics could not be completed. A full biomechanical analysis will be reported in future publications instead.

3.5.2.2 Grip Force

Rationale

Loss of grip force is a common impairment following stroke (Bohannon 1997, Boissy *et al.* 1999) and may reduce a person's ability to use their affected upper limb in ADL (Heller *et al.* 1987; Sunderland *et al.*, 1989; Boissy *et al.*, 1999). In a study with chronic stroke patients, Boissy *et al.* (1999) found that maximum voluntary grip force (MVGF) was significantly reduced in stroke patients. Furthermore, MVGF was highly and significantly correlated with four different arm function tests, including the arm section of the Fugl-Meyer (Fugl-Meyer *et al.*, 1975), which in turn is highly and significantly correlated with the ARAT (de Weerdt and Harrison, 1985).

Numerous tools and procedures for measuring grip force have been published, only to expose the effects of differences in methodology on the output (e.g. Su *et al.,* 1994; Kuzala and Vargo, 1992; Mathiowetz *et al.,* 1985; Richards *et al.*, 1996). Reviews of grip force measurement have highlighted the need for a standardised protocol (Richards and Palmiter-Thomas, 1996; Innes, 1999). In 1992, the American Society of Hand Therapists (ASHT, 1981) published standardisation guidelines, which have been followed by the majority of studies since.

For the study reported in this chapter, a Jamar dynamometer was used, which is a standard instrument in the measurement of grip force. High reliability has been reported for this instrument in stroke patients (ICC > 0.86, Boissy *et al.,* 1999), healthy subjects, as well as patients with cervical radiculopathy (ICC 0.85- 0.98, Peolsson *et al.*, 2001). There are normative data against which clinical data may be interpreted, which have been documented in a number of papers; e.g. subjects aged 60 and over (Desrosiers *et al.*, 1995) and subjects aged 20-64 years (Hanten *et al.*, 1999).

A calibration was carried out to determine the accuracy and precision of the Jamar grip force dynamometer (Appendix 3.5). The results indicated that these properties were satisfactory for forces equal to or greater than 107.8 N (11 kg), but that the accuracy and precision were unsatisfactory for forces of a lesser magnitude.

Protocol

The ASHT (1992) standardisation guidelines for the measurement of grip strength were followed (Appendix 3.4). The Jamar dynamometer was set at its second

handle position. Each participant carried out three attempts, first with the non-affected side, followed by the affected side.

3.5.2.3 Ashworth Scale (AS) with quantitative analysis of Resistance to Passive Movement (RTPM) and EMG (the DATA System)

Rationale

Similarly to the pilot study on botulinum toxin, reported in Chapter Two, the rationale for including the Ashworth Scale (Ashworth, 1964) was to be able to compare the effects of the interventions on resistance to passive movement with the published literature. In contrast to the previous study however, the Ashworth Scale (as opposed to the modified AS) was used in order to avoid the ambiguity associated with the score of "1+", which was explained in section 1.2.4.2.

Additionally, as in the pilot study, the DATA system (Pandyan *et al.*, 2001, 2003) was used to quantify and differentiate between biomechanical and neurological contributions to RTPM.

Protocol

The protocol for applying the DATA system and collecting the data was the same as for the pilot study (Chapter Two), except for the type of instrument for recording EMG, which was not available for the present study. Instead, a Biometrics Ltd. surface EMG system was used. This consisted of a lightweight, pre-amplified SX230 surface EMG sensor (mass 12 g, inter-electrode distance: 20 mm[2], diameter: 10 mm, gain: 1000, bandwidth: 20-450 Hz, noise: < 5μV), connected to a DataLINK, which in turn was connected to a computer. The ground reference cable was connected to an elastic wrist band, with the reference electrode placed on the ulnar styloid. The input impedance was such (>10^6 M Ohms) that, according to the specifications, only little skin preparation and no gel were required. Although more recent guidelines on the application of EMG (SENIAM project) emerged after the study had commenced, the procedures used in previous studies with the DATA system (Pandyan *et al.*, 2001, 2002) were adhered to, in order to obtain comparable

[2] Inter-electrode distance: measured from centre to centre.

results. The RTPM encountered during the Ashworth Scale was scored according to the criteria listed in Box 3.4.

Box 3.4
Scoring criteria for the Ashworth Scale (Ashworth, 1964)

Score	Criterion
0	no increase in muscle tone
1	slight increase in muscle tone giving a „catch" when the limb was moved in flexion or extension
2	more marked increase in muscle tone, but limb easily flexed
3	considerable increase in muscle tone – passive movement difficult
4	limb rigid in flexion or extension

3.5.2.4 Stroke Impact Scale

Rationale

In order to obtain the views of study participants on the effects of the intervention, the Stroke Impact Scale, Version Three (SIS-v.3, Duncan *et al.*, 2003) was selected. This is a self-report measure, which is administered in interview form, while a subsequent study with the SIS-v.2 indicated that administering the SIS by mail was also feasible, with omissions being relatively infrequent (Duncan *et al.,* 2002). The SIS has been developed on the basis of interviews with stroke patients, their carers and health care professionals (Duncan *et al.*, 1999, 2001) and covers the following domains: strength of the affected limbs, gait, stair climbing and transfers, ability to use the affected hand in ADL, independence in general ADL, participation in leisure, voluntary activities and paid employment, cognition, emotion and communication, as well as overall recovery. Apart from the last item, which is scored on a vertical visual analogue scale, each item is scored on a five-point ordinal level scale (Appendix 3.4).

In order to obtain a comprehensive picture of the study population at baseline, all SIS items were reported for week 0. In terms of outcome measures, the items pertaining to ADL (SIS-5), hand function (SIS-7) and participation (SIS-8) were deemed to be most appropriate: although strength of the affected arm would have been of interest, its score was combined with sub-items on strength of the affected leg and could therefore not be distinguished. Items on cognition, emotion and communication were omitted as these did not relate to the aims of the intervention. The item referring to "overall recovery" was also omitted, given the specificity of the

intervention programme and the findings from the literature, discussed in section 1.3, which had indicated a lack of impact on global function (Bakheit *et al.,* 2000, 2001; Simpson *et al.,* 1996).

Duncan *et al.* (1999) reported the validity, reliability and sensitivity to change of the SIS-v.2. In terms of criterion validity, the correlations between domains of the SIS-v.2 and those of established tools (e.g. the Barthel Index, FIM, SF-36) showed that correlations pertaining to ADL were very high, but those pertaining to cognition, communication and participation were lower. Test-retest reliability ranged from moderately high to very high (ICC 0.70-0.92), with the exception of the emotion domain, which was only moderately reliable (ICC 0.57). The measure appeared to be responsive to change between one, three and six months following stroke, with a change between 10 and 15 points being considered as clinically meaningful. Duncan *et al.* (2003) then performed a Rasch analysis on the SIS-v.2. Five items were deleted to yield the SIS-v.3, with 61 items divided over eight uni-dimensional domains. Overall, this analysis showed that the items were representative of the problems most frequently experienced by the target population, further supporting the construct validity of the tool. Additionally, the scores in each domain enabled different levels of stroke severity to be distinguished. Although the psychometric properties of the SIS-v.3 are generally favourable, it was unclear whether its responsiveness would be sufficient for the stroke population from which the current study was to recruit. In contrast to the sample on which the SIS was based (i.e. people with mild or moderate stroke between 14 days and six months after the acute event), the target population for the current study was expected to comprise mainly those in the chronic stage after a moderate to severe stroke. A property in favour of the SIS was that, in comparison with the Barthel Index, it did not suffer from ceiling effects – on the contrary, the SIS-v.2 was still able to demonstrate deficits in hand function in those where the Barthel Index suggested complete recovery (Lai *et al.*, 2002). Lai *et al.* (2003) also demonstrated the physical and participation domains of the SIS-v.2 to be superior to the corresponding domains of the SF-36. Importantly, compared to the Barthel Index and the Rankin scale, the SIS-v.2 included a wider range of issues, providing more comprehensive data on the impact of stroke (Duncan *et al.,* 1999).

Taken together, the SIS appeared to be a more stroke-specific and comprehensive scale and therefore more suitable for the present study than any of the more general, global disability scales.

Protocol

In order to prevent over-assessment, participants were asked to complete the SIS at home and return their response in a pre-paid envelope. The purpose and content of the scale were explained face to face beforehand, according to the guidelines issued together with the instrument (Duncan *et al.,* 2003). Participants were advised to contact the assessor by telephone if they had a query. In the case of a non-response within one week of issuing the SIS, or where missing values were found on a returned questionnaire, participants were contacted by telephone to address the issue.

3.5.2.5 Participants' perspectives

Rationale

In addition to investigating any treatment effects in terms of standard outcomes, the study also sought to explore each participant's personal perspective on both the outcomes and the processes involved in the intervention. To address the former, the Canadian Occupational Performance Measure (to be detailed in section 3.5.5) had been selected. To explore the latter, informal comments from the participants during treatment and assessment, as well as comments from the research physiotherapist were noted.

Protocol

Comments from participants, as well as the research physiotherapist during the treatment programme, were written down by the therapist in her case notes. This information was only relayed to the assessor (fvw) after the data analysis stage had been completed and blinding of the assessor had been removed. Comments from the participants were also noted by the assessor upon follow-up. In order to ensure continued blinding, participants were reminded at the start of each assessment that they were not permitted to mention anything in relation to the type of treatment they had received. Using open questions throughout, they were asked for their opinion on the frequency and duration of the intervention programme, in order to gauge the

burden of the treatment schedule *per se.* Additionally, they were asked whether they had experienced any adverse effects. Finally, participants were asked if they had noticed any changes from the previous assessment or any differences compared with their usual BTX-A treatment. Any other spontaneous comments were noted also.

3.5.2.6 Line Bisection

Rationale

Neglect is a common problem following a stroke (Stone *et al.*, 1992). It was thought that neglect could be a potential confounding variable for participants in the experimental group, which required sustained and focused attention to and action of the affected upper limb in contralateral space. To identify the degree of neglect, the Line Bisection item from the Hemispheric Stroke Scale (Adams *et al.*, 1987) was carried out at baseline (week 0) only.

Protocol

Each participant was asked to bisect a line (length 20 cm) long (Appendix 3.4). If the participant bisected the line more than 0.5 cm (Platz et al., 1999) in the direction of the non-or less affected side of the body, he/she was presented with a second and a third line to check if this deviation was consistent. If similar results were obtained, the participant was asked whether she/he felt that the affected side belonged to her/him and whether she/he had any difficulties using the affected arm. If this was confirmed, it would be noted on the test form as "neglect".

3.5.2.7 Visual Movement Imagery Questionnaire

Rationale

In order to evaluate the participant's ability to visualise movement, the Vividness of Movement Imagery Questionnaire (VMIQ, Isaac *et al.*, 1986) was selected. This test was completed at baseline (week 0) only, as the purpose of it was to explore whether this was a covariate in the study, as had been suggested in a study by Eton *et al.* (1998). The VMIQ consists of 24 items, which require the participant to visualise either themselves or a third person performing an activity. The rating for

each activity is indicated on a five-point ordinal level scale. In terms of its psychometric properties, Eton *et al.,* (1998) found the VMIQ to be superior to the Vividness of Visual Imagery Questionnaire (Marks, 1973, cited in Eton *et al.,* 1998), which addresses a similar, but not identical construct. Internal consistency was found to be acceptable, with α being equal to 0.96 for both sub scales and 0.97 for the total scale (Eton *et al.,* 1998). Test-retest reliability was found to be moderately high to high[3] (r=0.76 over a three-week interval (Isaac *et al.*, 1986) and between 0.64 and 0.80 over a two-week period (Eton *et al.,* 1998)). However, Eton *et al.,* (1998) argued that imagery vividness might not be a stable trait to begin with. Normative data pertaining to students with different levels of engagement in athletics, were reported by Eton *et al.* (1998).

Protocol

The protocol outlined by Isaac *et al.* (1986) was followed (Appendix 3.4). To avoid over-assessment, participants were given this test as a questionnaire to complete at home, after the procedure had been explained face to face. To aid this process, explanatory information had been included at the start of the questionnaire and participants were advised to contact the assessor by telephone in case they had any problems. There was no indication in the literature at the time of the study on the reliability of this form of administration.

3.5.3 Botulinum toxin type-A treatment

Similar to the pilot study in Chapter Two, BTX-A was administered by clinicians, not otherwise involved in the study, following standard clinic procedures. Participants were either injected with Botox® (Allergan Ltd., High Wycombe, UK) or Dysport (Ipsen Ltd., Slough, UK), depending on their needs. Each vial of the toxin was reconstituted in 5 ml Normal Saline. EMG guidance was not used in this procedure. Following this intervention, participants were randomised according to procedures, designed to exclude any potential influence from staff involved in their BTX-A treatment or the actual trial, which will be described below.

[3] According to Nunally (1978), correlations are considered to be low for coefficients < 0.4, moderate for coefficients between 0.4 and 0.59, moderately high for coefficients ranging from 0.6 to 0.79, high for coefficients between 0.8 and 0.89, and very high for coefficients greater than 0.9.

3.5.4 Randomisation

Permuted block randomisation was used to ensure that the distribution of participants over the two treatment groups would be as balanced as possible, in case recruitment were to fall short of the target number. Procedures described by Beller *et al.* (2002) were followed. Each block consisted of four treatment allocations: two for the experimental and two for the control group. The order of treatment allocation within each block could be arranged according to six different permutations, which were selected randomly through a computer programme designed specifically for this study. Allocation concealment was achieved as follows: a mathematician, not involved in the study, generated a random number sequence with each number tied to a specific block permutation. The mathematician placed this sequence in an opaque envelope, which he sealed and rendered tamper-proof. The envelope was then handed to the clinic secretary, who was otherwise not involved in the study. The secretary was instructed to make up individual, opaque envelopes which were numbered, each containing one permuted block with the treatment allocation for four participants. The secretary then sealed each envelope, made them tamper-proof and stored them in a lockable filing cabinet until required. Implementation of the randomisation was carried out by the Clinic Nurse, who was otherwise not involved in the study. The Clinic Nurse was informed by the trial co-ordinator (fvw) each time a new participant had been recruited into the study. The Clinic Nurse would then look up the corresponding treatment allocation, which she communicated exclusively to the research physiotherapist, who provided the intervention. Whenever required, the Clinic Nurse would be given a new envelope by the secretary.

The secretary kept a record of which envelope was dispensed at what date, while the Clinic Nurse as well as the research physiotherapist kept their own records of each participant, their group allocation and the date at which they had been allocated. These records would enable the randomisation procedure to be checked at the end of the study. There was no communication between the assessor and the research physiotherapist regarding group allocation at any point in time and participants were explicitly instructed - and reminded prior to each assessment - not to provide the assessor with any information regarding their treatment at any time.

3.5.5 Physiotherapy assessment and goal setting (COPM)

All physiotherapy-related assessments and interventions were delivered by the same research physiotherapist. The therapist, a Clinical Specialist in neurological rehabilitation, had been qualified as a chartered physiotherapist for nearly 20 years and had worked in neurological rehabilitation for 16 years when the project started. She also had a postgraduate qualification in Disability Studies and had completed basic Bobath training and three advanced courses in this approach, as well a workshop in the Motor Relearning Programme approach.

The research physiotherapist met with each participant on day one of Week 0, before the start of the intervention. The aims of this session were to carry out a physiotherapy-specific assessment, set goals with the participant and provide information on the content and procedures of the treatment programme. A written summary was issued to participants for reference (Appendix 3.3). This assessment was carried out in line with normal clinical practice in neurological rehabilitation and will not be further described.

In order to select a patient-centred outcome measure, several reviews were consulted (Donnelly and Carswell, 2002; Wade 1999a-d), which narrowed the choice to the Canadian Occupational Performance Measure (COPM, Law *et al.*, 1990) or the Assessment of Motor and Process Skills (AMPS, Goldman and Fisher, 1997, cited in Donnelly and Carswell, 2002). The former was selected for reasons identified below. Although an observational tool would have been preferred above a self-report measure, the AMPS required extensive formal training, which stretched beyond the resources that were available for this study.

Rationale

A preliminary pilot study with three participants who had had a stroke (Study 1A, Appendix 3.6) indicated that they found goal setting to be an invaluable part of the rehabilitation process. Therefore, it was considered to be important to include a formal tool in the study, which would assist participants in identifying their goals and registering change during the study.

Following an exploration of the literature on goal-setting, the Canadian Occupational Performance Measure (3rd edition, Law *et al.* 1998) was selected, as this had been well researched, had favourable psychometric properties, appeared to be practicable and had been used with people who had had a stroke. The COPM,

developed by the Canadian Association of Occupational Therapists in association with Health and Welfare Canada (Law *et al.*, 1990), is based on the Canadian Model of Occupational Performance. The COPM is designed to help participants define their own treatment goals through a semi-structured interview. The participant identifies and prioritises up to five issues related to self-care, leisure and productivity and scores each one in terms of their perceived performance as well as satisfaction with their performance. For each issue, scores range from 1 to 10, with a higher score indicating a more positive rating (Appendix 3.4). With the COPM being a patient-centred outcome measure, it is not norm-referenced.

A comprehensive literature review of the COPM, published by Carswell *et al.* in 2004, yielded 19 studies on the psychometric properties and utility of the tool, as well as evidence of its broad application in different research and health care settings. Eleven studies investigated the validity of the COPM. A study by Chan and Lee (1997), involving orthopaedic as well as stroke patients, supported the content validity of the COPM but failed to confirm convergent validity between the COPM-Performance dimension and FIM-motor subscale. This suggested that the tools addressed different constructs. Indeed, in terms of discriminant validity, studies involving stroke patients by Cup *et al.* (2003) and Dedding *et al.* (2004) established the discriminant validity of the COPM by showing low correlations between the COPM and five different functional measures (including the Barthel Index and the Sickness Impact Profile). These results clearly demonstrated that the COPM yielded information that could not be obtained from standard outcome measures.

Only four studies reported on the reliability of the COPM, which generally appeared to be robust. For example, the study by Cup *et al.* (2003) showed that test–retest reliability (with a mean interval of eight days) was high for the Performance scores (Spearman's $\rho = 0.89$, $p<0.001$) as well as for the Satisfaction scores ($\rho = 0.88$, $p<0.001$). However, the goals themselves appeared to change over time, with only 56% of the originally identified goals being listed on the second occasion.

Responsiveness to change was evaluated in five studies, which generally indicated that the COPM was more sensitive than other, standardised and more general outcome measures (e.g. the Reintegration to Normal Living Index: Eng *et al.*, 2003 and the SF-36: Case-Smith, 2003).

Interestingly, Simmons *et al.* (2000) demonstrated that the predictive power of the FIM could be enhanced by including information from the COPM.

The literature on the clinical utility of the COPM (i.e. ease of administration, acceptability of format, usefulness of information) was mixed (Toomey *et al.,* 1995; Dedding *et al.,* 2004), although therapists appeared to agree on the value of the tool. McColl *et al.* (2000) reported that participants themselves found the COPM useful and easy to use. However, since there were no details on the nature of participants' pathologies, it was not possible to gauge whether people in the chronic stage after stroke, possibly with some cognitive or communication impairments, would find the tool easy to use. Therefore, the COPM was implemented in a preliminary pilot study with two participants (Study 3B, Appendix 3.6), who reported that the tool had been helpful to identify their goals. Additionally, the study by Dedding *et al.* (2004) included stroke patients whose views on the tool were also favourable.

The COPM has been used in a wide range of settings, including occupational therapy within a neurological rehabilitation unit (Bodiam, 1999) and with older people in the community following a stroke (Reid *et al.,* 2001, in Carswell *et al.,* 2004), as well as following botulinum toxin therapy in children with cerebral palsy (Wallen *et al.,* 2004). However, at the time of the study, there were no publications detailing its application to upper limb spasticity management in people in the chronic stage after stroke. The principal author of the COPM was contacted to obtain permission to: 1) use the tool for the particular purpose of the study, and 2) have it implemented by a physiotherapist. Permission was obtained for both points (Law, personal communication, November 2002).

Protocol

The standard COPM protocol, as described by Law *et al.* (1998), is included in Appendix 3.4. The treating therapist administered the COPM. It was acknowledged that this might induce bias, but given resource constraints it was not possible to involve an independent member of staff in this process. The COPM was administered at baseline (Week 0), in the week following the end of the program (Week 4) and at the final assessment (Week 13). Week 7 was omitted, as this point in time was not expected to be sufficiently informative to warrant the logistic complexity of scheduling an additional appointment to administer the test.

3.5.6 Intervention

The intervention strategies for both the experimental (EG) and control groups (CG) were piloted before they were implemented in this RCT. The various decisions that were made (e.g. regarding the duration and frequency of the programme, the types, number and level of difficulty of the therapeutic activities, the content of the mental practice protocol and the details of the stretching protocol) will be indicated in the respective sections. The details of this preliminary pilot work can be found in Appendix 3.6, as well as in a number of preliminary publications (van Wijck *et al.*, 2004[a], 2004[b], 2005, 2006[a]).

As described in section 3.5.4, participants in both groups received their BTX-A treatment on one occasion from an independent clinician at HM. To minimise confounding variables, the duration, frequency and location of all intervention sessions following BTX-A were identical for both groups, i.e. 60 min. per session, on five weekdays per week, for three consecutive weeks. These parameters were selected as they fell within the boundaries of similar interventions (reviewed in section 1.5). Additionally, they were based on pragmatic decisions: less than a one-hour session was deemed to be insufficient to achieve the treatment goals, whereas a duration of more than one hour was thought to exceed participants' exercise tolerance. Five weekdays per week was deemed to be necessary to achieve a sufficient level of intensity, which had been recommended in the literature (see section 1.5.3). Three weeks for the overall programme had been selected since two weeks was estimated to be too short, while four weeks was considered to be too burdensome. Preliminary pilot work confirmed that these parameters were tolerable by the participants (Appendix 3.6, studies 3A, 3B and 3C).

The same research physiotherapist delivered all the intervention sessions. Each session commenced with a standard set of passive stretching and mobilisation techniques for 15 min. (section 3.5.6.1 and Appendix 3.10). This component was included since it is standard practice at HM to advise all patients, who have been treated with BTX-A, to carry out self-stretching exercises on a daily basis.

Following on from the preparatory stretching, those in the EG participated in a 45 min. active, functional motor learning programme, which is described in more detail

in section 3.5.6.2. In contrast, the CG rested their affected upper limb in an air splint while seated at a plinth (section 3.5.6.3).

3.5.6.1 Preparatory Stretching

Prior to each treatment session, all participants were given soft tissue stretching and mobilisation of their affected upper limb. In order to inform the protocol, a literature search was carried out on this topic[4]. This, however, yielded a dearth of relevant information – an impression confirmed by Edwards (2003, personal communication). Therefore, a protocol was developed on the basis of the available literature and pilot work involving a consensus meeting with physiotherapists experienced in neurological rehabilitation at HM (Appendix 3.9). To summarise, the entire procedure was designed to last 15 minutes. It would commence with mobilising the trunk and scapula, then work towards distal joints, before a whole upper limb stretch was carried out. The duration of most of the stretching procedures, of which four repetitions were administered, was 20 seconds each (Carr and Shepherd, 2003). As for stretching the forearm pronators or supinators, one option was selected, depending on what each participant required. Stretching was administered by the research physiotherapist in order to ensure consistency of input. Participants, who were in a seated position, were encouraged to relax as much as possible during this component of the intervention.

[4] Databases searched were: CINAHL and MEDLINE for keywords "stretching" AND "review", "stretching" AND "stroke", ", "stretching" AND "upper limb", from start of the database to February 2003. In addition, standard neurological physiotherapy textbooks, sports science literature, as well as *PhysioTools – Neurology* were explored.

3.5.6.2 Experimental Group

Introduction

This section presents the protocol for the skill acquisition programme for participants in the experimental group. The rationale for this programme was developed in sections 1.5 and 1.6.

Goals and Activities

With regards to the *types of goals*, preliminary pilot work with participants in a similar condition (Study 1B, Appendix 3.6) revealed that the goals should centre around the following categories of activities:

- pick-and-place functional objects,
- grooming,
- dressing and feeding,
- bimanual functional activities.

Hence, these activities were selected to form the core of the programme. In order to render the intervention more relevant to each participant and to encourage motivation, each participant also chose one optional goal. This was identified by means of the COPM (Law *et al.*, 1998), as described in section 3.5.5, before the intervention commenced.

With regards to the *level of difficulty*, the data from the Botulinum Toxin pilot study, reported in Chapter Two, were revisited (table 2.7). These showed a median ARAT score of 3 points (range 0-11 points) at baseline, which indicated that most participants were unable to perform any activities requiring hand function. Thus, the participants to be recruited into this study (who were to be drawn from a similar population) were also expected to present with severely impaired arm function. Therefore, the tasks needed to be set at a level that would be feasible, yet challenging and enjoyable, for all participants including those with a minimum of hand function.

With regards to the *number of activities* and the *duration* per session, preliminary pilot work (Appendix 3.6, study 3A) suggested that the maximum number of tasks (each to be repeated three times) included in each session should be five. A 45-minute session was felt to be challenging but manageable, provided that adequate rest periods were included after each set of activities.

Taken together, the programme included the following activities:

1. Reach and grasp functional object, pick up, place, release (e.g. pick up mug from a specified location on the table top and transport to other location).
2. Reach and touch specific upper body location (e.g. wipe nose)
3. Reach for upper body garment, don, adjust or doff garment (e.g. adjust neck of cardigan, don mitt).
4. Stabilise object with affected hand while manipulating this with the less-affected hand (e.g. stabilise note block with affected hand, write with the non-affected hand).
5. Optional activity.

During any of these activities, participants could be either in a sitting or standing position, which was indicated on the protocol.

The categories of tasks, their variations and order were the invariants of the programme and were determined *a priori*, whereas the details of objects to be used were fine-tuned by the research physiotherapist according to the individual capabilities of each participant at each session.

A full description of the skill acquisition programme and details pertaining to the tasks are included in Appendix 3.7.

Structure of the three-week programme

Fig. 3.5 outlines the overall structure of the three week skill acquisition programme. The programme as a whole had been designed to facilitate problem solving and independence in carrying out selected activities of daily living. Therefore, each week involved a progression in terms of information processing by increasing contextual interference and reducing augmented feedback, based on the literature presented in section 1.6. At the same time, the mechanical load was progressed as the research physiotherapist selected more challenging objects (in terms of their weight and dimensions) or increased the height and/ or distance over which the participant had to reach.

Preliminary pilot work was carried out (Appendix 3.6, studies 3A and 3B) to test the feasibility of the entire three-week programme. The findings from study 3B served to reinforce adherence to the eligibility criteria. The results from study 3A indicated that, although both participants in study 3A experienced the schedule as intensive, they also found the intervention to be relevant, challenging and enjoyable. The

component that both participants found to be most valuable was thinking about how they could enhance the involvement of their affected arm in every day activities. The results, in terms of outcomes, were also promising (van Wijck *et al.*, 2004a, Appendix 6), although it needs to be emphasised that these case studies were not placebo-controlled and therefore open to experimenter bias. The final protocol is included in Appendix 3.7.

Each day of the programme followed a unique protocol (for specimens, see Appendix 3.7). Tasks for each day had been selected randomly following a computer algorithm (Appendix 3.8). Fig. 3.6 outlines the generic template for each session.

Demonstration

Before starting practice proper, each activity for that session would be demonstrated to enable the participant to obtain an accurate image of the activity and to activate the neural networks that would be involved in overt practice. This was achieved through a standardised process, which started off with a demonstration from the research physiotherapist, which was then repeated by the patient in the following order: one trial with the non- or less-affected side, then one bilateral trial (in cases where the task was unimanual and unilateral). These two trials were included to facilitate performance of the affected side by activating the required template for action involving the non-affected side (Mudie and Matyas, 2000). Having completed this, the participant then performed one trial with the affected side without manual guidance so that the therapist could ascertain which problems needed to be addressed. Finally, the participant attempted one trial with the affected side with manual guidance from the therapist so that the participant was left with an optimal image of task performance before starting practice proper.

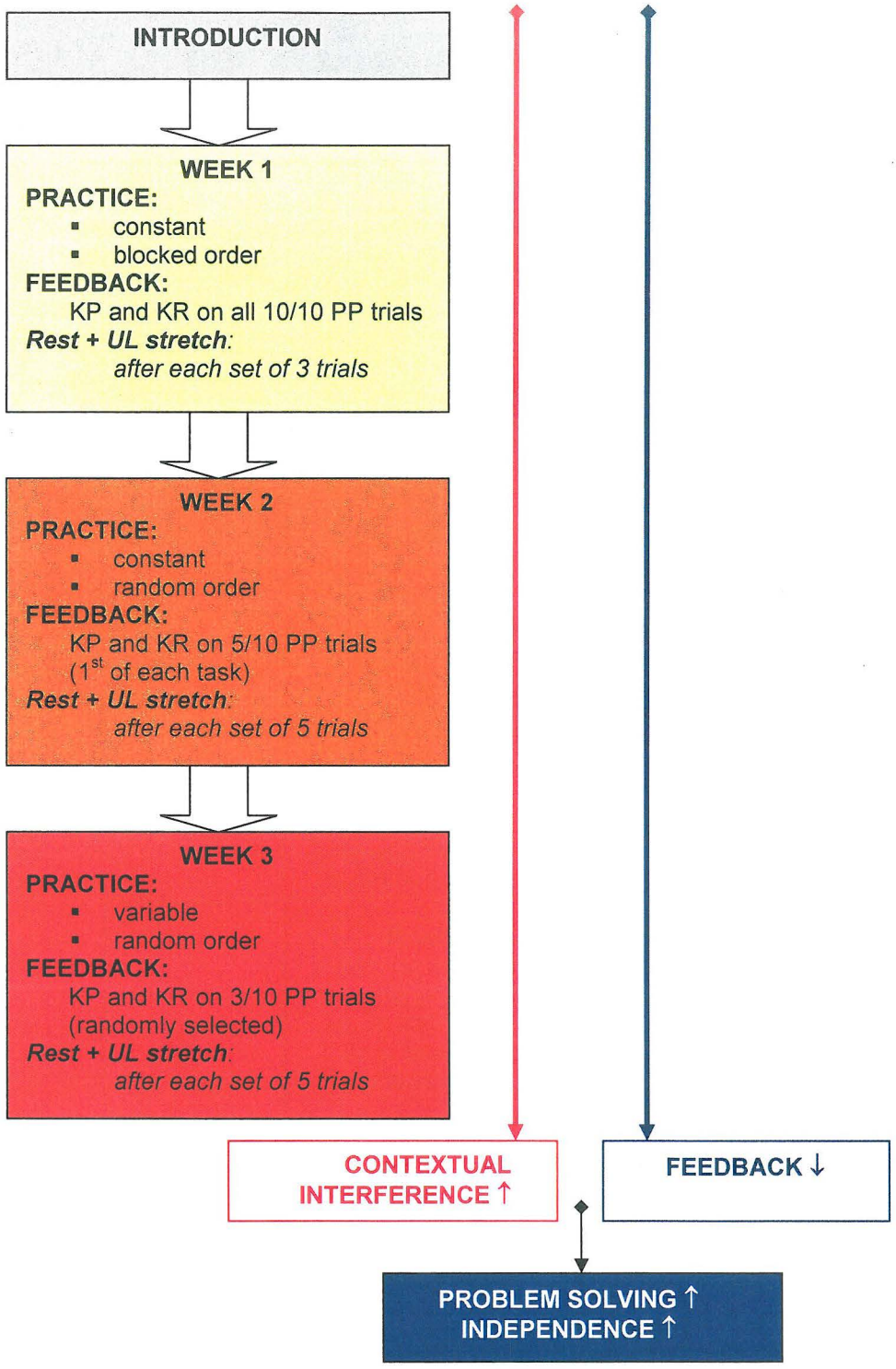


Figure 3.5
Overall structure of the skill acquisition programme
KR: knowledge of results; KP: knowledge of performance, PP: physical practice, MP: mental practice, UL: upper limb

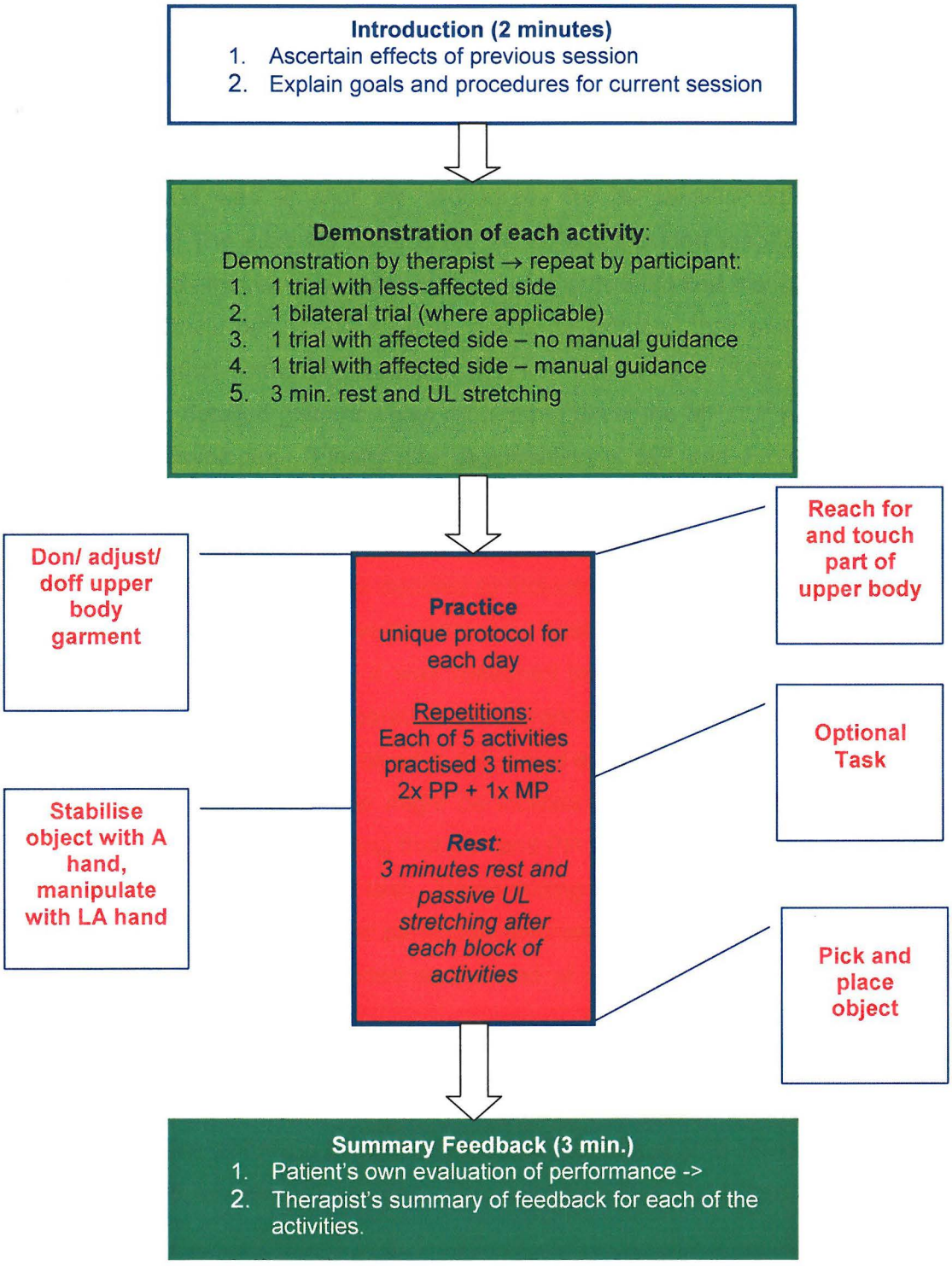


Figure 3.6
Template of each 45-min. skill acquisition session for the Experimental Group
A: affected side; LA: less (or non-) affected side; UL: upper limb. PP: physical practice, MP: mental practice.

Type of practice

In the first therapy session, the research therapist explained that both physical (PP) and mental practice (MP) would be used. The mental practice protocol was developed during preliminary pilot work, described in Appendix 3.6. The first aim of this was to gauge, in an informal manner, the attitudes of participants regarding MP and the second was to pilot the procedures for its administration (Study 2A, Appendix 3.6). The *attitudes* towards MP varied and included scepticism, curiosity, recognition and amusement. Most of the participants indicated that an explanation about the rationale behind this strategy helped to increase their motivation. They also indicated that some familiarisation with MP was needed. With regards to its *administration*, detailed guidance was required to direct the MP, for which standard scripts were developed. Finally, the *organisation* of MP and PP needed to be established. Based on the study by Hird *et al.* (1991, see section 1.6) indicating the superiority of PP over MP, together with the practicality that each category of activity would only feature thrice, it was decided to include two trials of PP and one trial of MP. Next, their order had to be determined. Based on the literature presented in sections 1.5.2.8 and 1.5.2.11, it was reasoned that the benefit of MP would be derived primarily from the preparation of the required motor programme and from priming the neural networks involved in the actual execution of the task. It was also thought that in actual ADL, one might be inclined to mentally "go through" a task prior to carrying it out, suggesting that MP and PP should be combined so that MP would precede PP of the same task. When putting this to the test (Preliminary pilot study 2B, Appendix 3.6), the one participant involved confirmed this suggestion.

The final MP protocol is included at the end of the skill acquisition programme (Appendix 3.7).

Thus, in the actual study, the rationale for MP was explained in the first treatment session, in order to inform and motivate participants. The participant was then introduced to this technique by mentally practising an upper limb activity, after which the research physiotherapist addressed any questions that might arise.

Organisation of practice

Table 1.8 lists definitions of the practice and feedback schedules used in the programme. On each day of Week One, one variation of each task was practised only (i.e. constant practice). Each of the five tasks was practised in blocked order to facilitate the development of a consistent image of the task (Schmidt and Lee, 1999). Thus, on each day, the participant practised three trials of each task before progressing to the next one. Each block consisted of one trial of PP, then one trial of MP on the same task, which was followed by one more trial of PP. Each block was interspersed with three minutes of rest, during which the therapist stretched the affected UL muscles, using the total UL stretch described in Appendix 3.10. For every day of the Week One, the order of the blocks was randomised, using computer-generated random numbers (Appendix 3.8).

In Weeks Two and Three, participants were estimated to have completed the cognitive stage of learning. In order to facilitate deeper learning and problem-solving and enhance transfer to ADL, tasks were practised in random order (Schmidt and Lee, 1999; Magill 2001). To ensure a gradual increase in complexity however, tasks in Week Two were kept constant, whereas variations were used in Week Three. Variable practice was achieved by using different start and end positions and/ or different objects (where applicable).

Tasks were selected from the list of variations in Appendix 3.7 by means of a computer algorithm (Appendix 3.8). In order to increase strength and endurance, the number of tasks within each block increased from three in Week One to five in Weeks Two and Three, whilst the total number of tasks carried out per session (i.e. 15 following demonstration) remained the same throughout. Half of the PP trials were preceded by one MP trial of the same task, in order to facilitate motor planning. This implied that in Week Three, the participant practised, in random order, two different variations of each task. At the start of each session, the therapist demonstrated both variations of each task. Tasks were always practised in their entirety (i.e. "whole practice", as opposed to "part practice") as this was more likely to transfer to the whole task for discrete as well as continuous skills - although practising difficult parts might have been more effective for serial tasks (Schmidt and

Lee, 1999). To enhance standardisation, a "whole practice" approach was taken for the entire programme.

Amount of practice

Following the demonstration, where subjects attempted each task four or five times (four times if bilateral practice was not appropriate) with the non-affected as well as the affected side, each category of tasks was then practised three more times with the affected side (i.e. twice using PP and once using MP) during each session. Based on pilot work, described in Appendix 3.6 (study 3A), this number of trials had been found to be a realistic for a 45-minute session. Thus, in total, each category of tasks featured between seven and eight times per session, which equalled between 105 and 120 times over the programme as a whole.

Organisation of Augmented Feedback

Augmented feedback from the therapist comprised KP (knowledge of performance - movement related) and KR (knowledge of results - outcome related). With regards to KP, information was given on the movement pattern, while in terms of KR, information on endpoint error and/ or time from start to end was provided. In order to develop independent problem solving, a fading feedback design was used (Schmidt and Lee, 1999) as follows: in Week One, feedback was given on all PP trials (i.e. 10/10 trials). In Week Two, feedback was given only after each first trial of PP of each task (i.e. 5/10 trials). In Week three, feedback was further reduced and only provided on 3/10 randomly selected trials of PP.

Manual guidance was provided minimally during the first PP trials of each activity within each session, with the sole purpose to enable the participant to form a clear image of the task (Schmidt and Lee, 1999). During the final PP trial, no manual guidance was provided to allow the participant to perform the activity independently and learn from any errors that might occur.

Equipment

In order to enhance transfer, tasks were occupationally embedded, i.e. tasks were not simulated but were carried out as in real-life ADL. Functional objects were used, e.g. participants were asked to bring their own personal items for some of the dressing/ grooming tasks. Appendix 3.7 lists the range of objects that were used.

3.5.6.3 Control Group

Introduction

In order to provide a contrast with the active condition in the EG, the CG remained passive, which was achieved by the application of an inflatable upper limb pressure splint. The purpose of the splint was merely to stabilise the limb in the position achieved at the end of the stretching programme.

The absence of any treatment effects of this technique had been reported by Poole *et al.* (1990), who used an inflatable upper limb splint with 18 chronic hemiplegic patients in a study where the treatment duration and frequency (i.e. 30 minutes per day, five days per week for three weeks), were similar to that of the current study. At 24 hours after the end of treatment, the findings indicated that there was no significant change in upper limb sensation or motor scores. Taken together, the inflatable upper limb splint was considered to be a suitable placebo condition for the present study. This technique had also been used in a study by Kwakkel *et al.* (1999) as a placebo.

Protocol

The splinting technique was originally described by Johnstone (1995) and is taught in specialist courses. However, enrolling in one of these courses was beyond the scope of the current project and on the basis of the literature only, it was difficult to establish whether the technique was applied correctly. Therefore, expert advice was sought and obtained from Superintendent Physiotherapist Ms. Smith at Alnwick Hospital, Alnwick, UK, an accredited Johnstone instructor (28/02/03). Preliminary pilot work was carried out in order to establish a suitable methodology (Appendix 3.11).

Materials

The inflatable upper limb splint (Urias ® Pressure Splint, long arm, 1 chamber, 30") was used. Manufacturer's instructions were followed throughout. The participant's arm was dressed in a thin cotton sleeve, which acted as a protective layer between the participant's skin and the splint. An adequate number of pillows or other support material was used to ensure correct positioning of the participant for safety and comfort through the application of the splint.

Procedure

Contra-indications

Contra-indications were checked before the splint was applied, as indicated in the manufacturer's instructions. It was envisaged that some participants might not tolerate the whole arm splint. In such cases, as advised by Smith (personal communication, 2003), the splint would be removed and a half arm splint (Urias ® Pressure Splint, half arm, 1 chamber, 20") would be donned instead. In cases where the participant did not tolerate this either, he/she would discontinue the trial.

Duration

The entire procedure of donning, wearing and doffing the splint took 45 minutes, equal to the amount of time spent in skill acquisition programme by participants in the experimental group. The amount of time the patient spent with the splint on was approximately 30 minutes.

Further details pertaining to the preparation, splint application, checking up and aftercare are listed in Appendix 3.12.

3.6 DATA REDUCTION AND ANALYSIS

3.6.1 Primary and secondary outcome measures

Given the focus of the study, the following measures were considered to be the primary outcomes: ARAT (representing a standard UL function measure), COPM (representing a patient-centred outcome) and EMG (representing elbow flexor spasticity). The secondary outcome measures were: GF, RTPM, AS and SIS.

3.6.2 Data Distribution

The distribution of each dependent variable for both the EG and the CG was explored at each of the four assessment points with the Shapiro-Wilks test, as this tends to be more accurate than the Kolmorogov-Smirnov test (Field, 2000). In cases where the distribution of interval or ratio level data (i.e. EMG, RTPM, grip

force) emerged as significantly different from normal, measures of central tendency and variation were expressed as medians and interquartile ranges instead.

3.6.3 Dependent variables at each point of assessment

Action Research Arm Test (ARAT)

For each participant, a total ARAT score was compiled for their most affected arm by adding up the scores for the individual test items, as per original protocol (Platz *et al.,* 2005). From the total scores of all participants in each group, the median and interquartile range was computed to express group performance at each assessment point.

Canadian Occupational Performance Measure (COPM)

The COPM may yield a wide range of issues which may or may not be related to the upper limb. Given that the RCT concentrated on upper limb function, it was important to select only those issues that were directly related to the purpose of the intervention and exclude those that could be influenced by factors extraneous to the study intervention (e.g. employment, communication), as these would confound the results. In order to select upper limb-related issues, a decision tree was compiled (fig. 3.7). Following the COPM assessment, the research physiotherapist drew up a list with all the issues for each participant - but without their scores or group allocation - and sent this to the trial coordinator (fvw). The decision tree was then applied independently by the two raters, who decided whether an issue was upper-limb related or not. Their ratings were compared and in cases where there was a discrepancy, the treating therapist sent the researcher additional notes from herself or anonymous comments from the participant, which would place the issue in context. The decision tree would be applied once more and any remaining discrepancies would then be discussed until an agreement was reached.

As the number of issues, identified by each participant on their COPM, could vary between one and five, their scores were expressed in terms of a measure of central tendency instead of a total score, which would be influenced by the number of issues raised. As per protocol (Appendix 3.4), the participant rated each issue on two dimensions; i.e. the performance dimension (COPM-P) and the satisfaction dimension (COPM-S). Both the COPM-P and the COPM-S represented a scale with

scores ranging from a minimum of 1 to a maximum of 10 points. According to the original protocol, mean scores were to be calculated, but given the ordinal level nature of the COPM, median scores and interquartile ranges were computed instead. From the median scores of all participants in each group, the group median and interquartile range was determined.

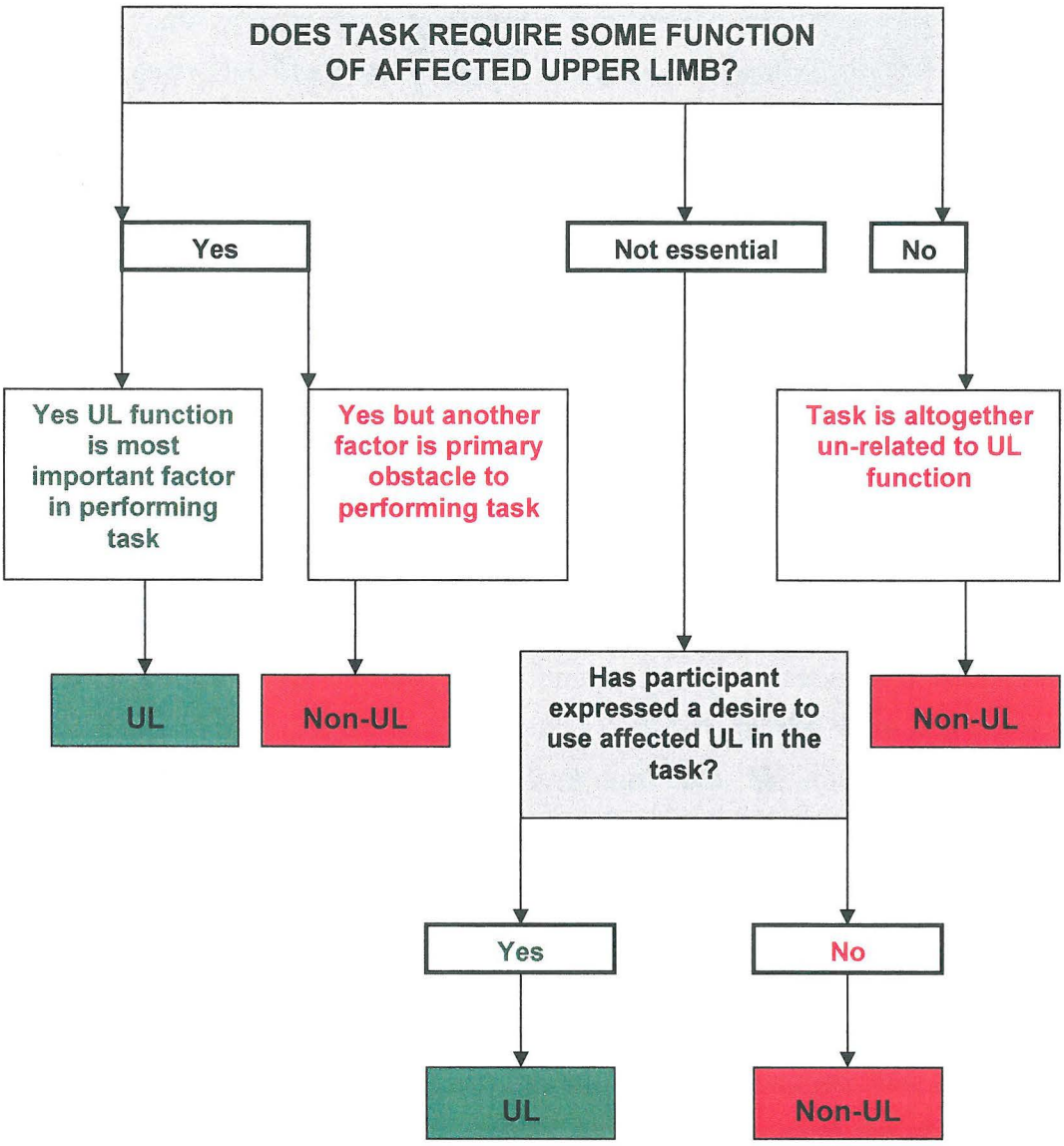


Figure 3.7

Decision tree for selecting upper limb (UL)-related issues from the Canadian Occupational Performance Measure (COPM).

Spasticity and RTPM Measures

Data pertaining to resistance to the Ashworth Scale, activity of the m. biceps brachii (EMG) and resistance to passive elbow extension (RTPM) during the Ashworth Scale were processed as described for the BTX-A pilot study in Chapter Two (see section 2.3.3.2). The only difference with respect to the RTPM data was that only 10-75% of angular displacement ROM was used, as opposed the full ROM, in order to avoid any artefacts associated with rapid acceleration and deceleration and the start and end of ROM, which had occurred during the pilot study.

Given the concern, raised in the literature (Bobath, 1969), that an increase in activity could trigger an increase in spasticity, the outcomes related to spasticity were assessed for the whole cohort – irrespective of whether BTX-A had been injected into the elbow flexors or not. The rationale was that both treatment conditions involved the entire UL and could potentially have an effect on any of these measures. An additional sub-group analysis was planned for those who were treated with BTX-A in the elbow flexors.

Grip Force (GF)

Grip force, measured in kilogram force, was converted into Newtons by multiplying the data by a factor of 9.8. For each participant, the mean and standard deviation of three attempts at each assessment was calculated, both for the more and the less affected hand. On the basis of these individual data, the mean and standard deviation were computed for each group.

Stroke Impact Scale (SIS)

The SIS was computed as per original protocol (Duncan *et al.*, 2003). For each participant, scores within each of the nine SIS domains were added up to yield a domain score. Although the data were expressed in percentages, they essentially represented ordinal level data. Therefore, for each participant the median and interquartile range was computed for each domain and from these data, the median and interquartile range was compiled for each group.

3.6.4 Within-group changes over time

For each participant, the change in each dependent variable was computed by subtracting the score at one point of assessment from that at a later point of assessment. From these data, the appropriate measure of central tendency and variation were computed to represent changes within each group over a specific period. Although these data will be described, they were not subjected to any further inferential statistics, since the focus of the study was on between-group differences in changes, as will be explained below. In addition, given the already considerable number of planned comparisons, it was important not to further inflate the experiment-wise error rate.

3.6.5 Between-group differences in changes over time

Having computed the change in each dependent variable for the EG and CG over specific points in time, the next step was to compare the differences in change between the two groups from baseline to week 4, baseline to week 7 and baseline to week 13.

In order to explore whether these differences reached statistical significance, inferential statistics were applied as follows. Where data were normally distributed, of interval/ ratio level and met all the necessary requirements, mixed models were planned (Brown and Prescott, 1999), as these provide advanced techniques for investigating between- and within-group changes over repeated assessments. In cases where the data were not normally distributed and/ or of ordinal level, non-parametric tests would be applied instead. SPSS version 12 (SPSS Inc.) was used for the statistical analyses. Alpha was set at 0.05.

3.5.6 Participants' Perspectives

As explained in section 3.5.2.5, the study also sought – in an informal manner - to explore each participant's own perspective on the outcomes, as well as the therapeutic processes involved in the study. From the notes taken during treatment by the research physiotherapist and during assessments by the assessor, the most

salient details, i.e. those that were felt to reflect the most important changes, astute observations or noteworthy experiences, were selected for inclusion in the results.

The findings from this exploratory trial will be presented in the next chapter.

CHAPTER FOUR

SKILL ACQUISITION AND BOTULINUM TOXIN FOR CHRONIC UPPER LIMB SPASTICITY AFTER STROKE: A FEASIBILITY RCT - *RESULTS*

4.1 INTRODUCTION

The primary aim of the feasibility RCT, described in Chapter Three, was to investigate whether there were any differential treatment effects from an additional skill acquisition programme following botulinum toxin type-A in terms of measures of activity or spasticity involving the affected arm. Following baseline assessment (Week 0), participants had been assessed on three further occasions: after the end of the therapy programme (Week 4), midway through the BTX-A cycle (Week 7) and at the end of this cycle (Week 13).

This chapter presents the results, starting with a description of the sample characteristics, performance at baseline and details of the BTX-A treatment. Next, within-group changes will be described for each group during each study phase, followed by a comparison of the differences between the two groups in terms of changes in each outcome measure. Additional details pertaining to participants' perspectives regarding outcomes and processes are included in Appendix 4.10.

4.2 SAMPLE CHARACTERISTICS

Table 4.1 presents an overview of selected demographic variables of the two study groups. More detailed information can be found in Appendix 4.1. Information on the distribution of the demographic data is provided in Appendix 4.2.

Despite very careful screening of all patients attending the weekly Spasticity Outpatient Clinic for a period of 12 months (April 2003 to April 2004), only 14 participants could be recruited. Of those who passed through to step 2 in the recruitment process (box 3.3), 37 people could not be recruited. The most common reason for non-eligibility was the absence of minimal hand function (n=13), followed by UL pain (n=2), health problems (n=2) and communication difficulties (n=1). One person was treated with BTX-B and one other did not require BTX-A. Others declined for the following reasons: inconvenience (n=6), concerns over transport (n=3), unavailable due to study or work (n=2), health problems of partner (n=1) and lack of interest (n=1). Three others could not be contacted by telephone. A modification of the eligibility criteria pertaining to hand function and verbal/ cognitive abilities was considered, but given the demands of the skill acquisition programme and the experience during preliminary pilot work (Appendix 3.6, study 3C), it was decided that it would not be ethical to widen the eligibility criteria.

Of the 14 participants recruited into the study, seven were randomly allocated to each group, following the procedure described in section 3.5.4. The average age of the EG was higher than that of the CG, with the CG including both the youngest (aged 29.3 years) and the most senior (aged 80.6 years) participants. The distribution of these data was not significantly different from normal in the EG or the CG group (Appendix 4.2) and an independent t-test indicated that the age difference between the two groups was not significant ($t=1.772$, $df=7.46$, $p=0.12$).
The sexes were distributed unequally across the groups, with no females in the EG and three in the CG. There were more right-than left-hemisphere lesions in the EG, whereas this was more equally divided in the CG. The distribution of ischaemic vs. haemorrhagic strokes was similar in both groups, with the first outnumbering the latter in both groups. In some cases, it was not possible to label the types of stroke

according to the Bamford classification (Bamford et al., 1991), due to a lack of information in participant notes. Time elapsed since the acute event was greater in the CG than in the EG, although there was considerable inter-subject variation in both groups. The distribution of time after stroke was not significantly different from normal (Appendix 4.2) and the difference in chronicity was not statistically significant (t=-1.32, df=12, p=0.21). In terms of hand dominance, most participants were right-handed in both the EG and CG. Two participants in the EG and three in the CG had changed their hand dominance after their stroke.

Table 4.1
Sample characteristics

EG: Experimental Group, CG: Control Group. Neglect: "Y": present or "N": not present. VMIQ: Visual Movement Imagery Questionnaire: "Other": as if visualising a third person and "Self": as if visualising self. VMIQ scores range from 120 (minimum) to 24 (maximum). MV: missing value. The last column indicates the level of significance of the difference between EG and CG for variables that were directly relevant for the study. NA: not applicable.

Demographics	EG (n=7)	CG (n=7)
Age (years): Mean (SD)	65.3 (6.2)	52.9 (17.5)
Range	56.4 - 74.4	29.3 - 80.6
Sex		
F	n= 0	n= 3
M	n= 7	n= 4
Time after stroke (years)		
Mean (SD)	4.5 (2.8)	6.8 (3.5)
Range	2.0 - 10.0	1.4 - 11.0
Affected hemisphere		
Right	n= 5	n= 4
Left	n= 2	n= 3
Type of stroke		
Haemorrhagic	n= 1	n= 2
Ischaemic	n=6	n=5
Hand dominance		
Before stroke		
Right	n=7	n= 6
Left	n= 0	n= 1
After stroke		
Right	n= 2	n= 3
Left	n= 5	n= 4
Neglect		
Yes	n= 1	n= 1
No	n= 4	n= 5
MV	n= 2	n= 1
VMIQ		
"*other*": Median (iqr)	**51 (93)**	**24 (12)**
Range	24 - 120	24 - 68
"*self*": Median (iqr)	**93 (96)**	**43 (53)**
Range	24 - 120	24 - 83
		MV: n=1

Neglect, assessed on the Line Bisection item of the Hemispheric Stroke Scale (Adams *et al.*, 1987), was only observed in one participant in each of the groups. Unfortunately, data were not available on two participants in the EG and one in the CG, as testing had been omitted in these cases to prevent overload.

Concerning participants' ability to engage in movement imagery, the Vividness of Movement Imagery Questionnaire scores (VMIQ, Isaac *et al.*, 1986) indicated that the EG found this considerably more difficult than the CG, both with regards to imagining a third person (i.e. VMIQ-other) and imagining oneself (i.e. VMIQ-self). The VMIQ-other scores from the CG were not normally distributed, with a concentration on the lowest scores (i.e. highest ability), whereas the distributions of the remaining VMIQ data sets were normal (Appendix 4.2). Mann-Whitney U-tests showed that the difference in the VMIQ-other score between the two groups was not significant ($U=10.0$, $p=0.12$) and the same applied to the VMIQ-self scores ($U=12.0$, $p=0.22$).

4.3 BASELINE (WEEK 0): PERFORMANCE AND OCCUPATIONAL ISSUES

4.3.1 BASELINE PERFORMANCE

An overview of the outcomes, assessed at baseline (week 0) is provided in Tables 4.2[a] and 4.2[b]. Statistics pertaining to the distribution of the data are listed in Appendix 4.2.

Several observations were noteworthy: both groups demonstrated considerable limitations on the ARAT, of which the maximum score is 57 points: both the EG and the CG had a median total score of 10 points (EG: range 4 to 46 and CG: range 5 to 37 points). The distributions of these data sets were significantly different from normal in both groups (EG: $p=0.07$, CG: $p=0.03$) with the data being negatively skewed. There was no significant difference between the two groups in terms of ARAT scores at baseline ($U=21.5$, $p=0.72$).

Table 4.2[a] Overview I of the dependent variables, assessed at Baseline (week 0).

EG: experimental group, CG: control group. ARAT: Action Research Arm Test, COPM-P: Canadian Occupational Performance Measure-Performance, COPM-S: Canadian Occupational Performance Measure-Satisfaction, EMG: EMG of the elbow flexors of the affected arm during the Ashworth test, RTPM: resistance to passive movement during the Ashworth test, AS: Ashworth Scale, GF Aff: Grip force of the affected hand (N) and Grip force Naff: grip force of non-affected hand (N), both expressed in mean and SD of three trials).

EG (n=7) Participant ID	ARAT Total	COPM-P Median	COPM-S Median	EMG (mV)	RTPM (N/deg) slope	RTPM (N/deg) r^2	Average speed (deg/s)	AS	GF Aff (N) Mean (SD)	GF NAff (N) Mean (SD)
3	4	2.0	1.0	1.916	0.18	0.82	61.1	3	11.5 (2.8)	346.2 (11.3)
6	4	3.5	3.0	1.905	0.46	0.91	21.9	3	71.8 (5.7)	352.8 (9.8)
7	13	4.0	3.0	1.881	0.69	0.94	38.1	1	78.4 (19.6)	352.8 (19.6)
10	4	2.0	2.0	1.841	0.11	0.82	111.7	2	6.6 (5.7)	258.0 (31.5)
11	46	3.0	4.5	1.924	0.09	0.80	143.8	0	83.3 (21.4)	421.4 (9.8)
13	13	2.5	4.0	1.889	0.11	0.82	73.9	1	59.6 (7.2)	414.8 (28.5)
15	10	3.0	2.0	1.819	0.72	0.94	41.0	2	39.2 (0.0)	339.8 (24.7)
Mean (SD)				**1.893 (0.030)**			**70.2 (43.7)**		**50.1 (31.6)**	**355.1 (54.3)**
Median (iqr)	**10 (9)**	**3.0 (1.5)**	**3.0 (2.0)**		**0.18 (0.58)**	**0.82 (0.12)**		**2 (2)**		
Min	**4**	**2.0**	**1.0**	**1.841**	**0.09**	**0.80**	**21.9**	**0**	**6.6**	**258.0**
Max	**46**	**4.0**	**4.5**	**1.924**	**0.72**	**0.94**	**143.8**	**3**	**83.3**	**421.4**
CG (n=7) Participant ID	**ARAT Total**	**COPM-P Median**	**COPM-S Median**	**EMG (mV)**	**RTPM (N/deg) slope**	**RTPM (N/deg) r^2**	**Average speed (deg/s)**	**AS**	**GS Aff (N) Mean (SD)**	**GS NAff (N) Mean (SD)**
2	6	4.5	2.0	1.865	0.08	0.09	17.5	3	42.4 (28.3)	365.8 (11.3)
4	6	3.0	3.0	1.889	0.65	0.86	86.4	3	58.8 (0.0)	251.6 (24.7)
5	13	2.0	1.5	1.926	0.25	0.98	115.6	2	88.2 (17.0)	441.0 (9.8)
8	37	1.0	1.5	1.817	0.18	0.92	48.4	2	137.2 (17.0)	506.4 (20.4)
9	10	4.0	7.0	1.895	0.64	0.93	18.4	3	45.8 (11.3)	392.0 (19.6)
12	5	8.0	8.0	1.868	0.23	0.92	112.5	1	39.4 (24.5)	253.7 (21.0)
14	11	1.0	1.0	1.857	0.23	0.87	146.79	1	6.6 (11.3)	196.0 (39.2)
Mean (SD)				**1.874 (0.034)**			**77.9 (50.8)**		**59.8 (41.9)**	**343.8 (113.4)**
Median (iqr)	**10 (7)**	**3.0 (3.5)**	**2.0 (5.5)**		**0.23 (0.46)**	**0.92 (0.07)**		**2 (2)**		
min	**5**	**1.0**	**1.0**	**1.817**	**0.08**	**0.09**	**17.5**	**1**	**6.8**	**196.0**
max	**37**	**8.0**	**8.0**	**1.926**	**0.65**	**0.98**	**146.8**	**3**	**137.2**	**506.4**

Table 4.2[b] Overview II of the dependent variables, assessed at Baseline (week 0)

EG: experimental group, CG: control group. SIS: Stroke Impact Scale (v3). Each SIS section pertains to a domain of body function, activity or participation. ADL: activities of daily living. Patient's self-report score for each domain was converted to a percentage score. MV: Missing value.

EG (n=7) Participant ID	SIS 1 Strength (arm + leg)	SIS 2 Cognition	SIS 3 Emotion	SIS 4 Communication	SIS 5 ADL	SIS 6 Mobility	SIS 7 Hand function	SIS 8 Participation	SIS 9 Overall recovery
3	56.3	100.0	77.8	100.0	55.0	52.8	0.0	62.5	60.0
6	50.0	64.3	63.9	82.1	37.5	55.6	0.0	43.8	40.0
7	50.0	75.0	86.1	75.0	72.5	91.7	25.0	81.3	70.0
10	50.0	75.0	88.9	82.1	42.5	86.1	0.0	71.9	50.0
11	62.5	78.6	55.6	67.9	85.0	72.2	30.0	25.0	60.0
13	62.5	60.7	83.3	67.9	50.0	38.9	0.0	40.6	40.0
15	50.0	42.9	58.3	82.1	65.0	75.0	10.0	28.1	50.0
Median (iqr)	**50 (12.5)**	**75 (17.9)**	**77.78 (27.78)**	**82.1 (14.3)**	**55.0 (30)**	**72.2 (33.3)**	**0.0 (25.0)**	**43.8 (43.8)**	**50.0 (20.0)**
Min	**50**	**42.9**	**55.56**	**67.9**	**37.5**	**38.9**	**0.0**	**25.0**	**40.0**
Max	**62.5**	**100.0**	**88.89**	**100.0**	**85.0**	**91.7**	**30.0**	**81.3**	**70.0**
CG (n=7) Participant ID	**SIS 1 Strength (arm + leg)**	**SIS 2 Cognition**	**SIS 3 Emotion**	**SIS 4 Communication**	**SIS 5 ADL**	**SIS 6 Mobility**	**SIS 7 Hand function**	**SIS 8 Participation**	**SIS 9 Overall recovery**
2.00	56.3	50.0	69.4	42.9	90.0	75.0	0.0	31.3	45.0
4.00	18.8	100.0	66.7	100.0	40.0	69.4	0.0	37.5	40.0
5.00	37.5	92.9	55.6	82.1	57.5	63.9	25.0	68.8	30.0
8.00	MV	MV	MV	MV	MV	MV	MV	MV	MV
9.00	43.8	100.0	83.3	92.9	65.0	77.8	0.0	40.6	65.0
12.00	37.5	89.3	55.6	96.4	42.5	52.8	0.0	18.8	20.0
14.00	62.5	75.0	80.6	92.9	55.0	77.8	0.0	46.9	40.0
Median (iqr)	**40.6 (25)**	**91.1 (31.3)**	**68.1 (25.7)**	**92.9 (25.0)**	**56.3 (29.4)**	**72.2 (16.7)**	**0.0 (6.3)**	**39.1 (24.2)**	**40.0 (22.5)**
min	**18.8**	**50.0**	**55.6**	**42.9**	**40.0**	**52.8**	**0.0**	**18.8**	**20.0**
max	**62.5**	**100.0**	**83.3**	**100.0**	**90.0**	**77.8**	**25.0**	**68.8**	**65.0**

There was no significant difference between the two groups in terms of elbow flexor EMG[1] (95% CI -0.128 to 0.191 mV, t=0.43, df=12, p=0.68).
In terms of resistance to passive elbow extension (RTPM) (analysed using a Mann-Whitney U test as its distribution was significantly different from normal in both groups), there were also no significant differences (U=23.5, p=0.93).
The average speed[2] at which RTPM was assessed varied considerably (table 4.2[a]), but there was no significant difference between the two groups (95% CI: -62.92 to 47.46 deg/s, t=-0.305, df=12, p=0.77). The Ashworth Scale (AS) indicated overall moderate resistance in both the EG (median= 2 points, range 0 to 3 points) and the CG (median = 2 points, range 1 to 3 points). These data were normally distributed in the EG, but there was a trend in the CG for the data to be skewed towards higher scores (p=0.06). There was no significant difference between the two groups with regards to the AS (U=19.0, p=0.58) at baseline.

Grip force (GF) was also severely impaired: on average, participants in the EG generated 50.1 N (SD=31.6) with their affected hand, which was approximately 14% of that generated by their non-affected hand. Those in the CG produced on average 59.8N (SD= 41.9), approximately 13% of that of the non-affected hand. The distribution of these data was not significantly different from normal and there were no significant differences between the two groups in terms of grip force of the affected hand (95% CI: -52.9 to 33.5 N, t=-0.490, df=12, p=0.63) or of the non-affected hand (95% CI: -96.9 to 119.6 N, t=0.239, df=8.62, p=0.82).

In the EG, all five participants returned their Stroke Impact Scale (SIS) questionnaire, while the response rate in the CG was six out of seven. Data from the SIS, Table 4.2[b] were also of interest, as they indicated that participants in both the EG and CG experienced relatively few difficulties in the domains of cognition (SIS-2), emotion (SIS-3), communication (SIS-4) and mobility (SIS-6). However, most participants indicated problems in the domains of strength in the affected arm and leg (SIS-1), activities of daily living (ADL, SIS-5) and participation (SIS-8), while

[1] EMG data were analysed with an independent T-test, as the Shapiro-Wilks test indicated no significant difference from a normal distribution (EG: p=0.75, CG: p=0.94, Appendix 8.2) and equal variances could be assumed, as Levene's test was not significant (p=0.69).
[2] Speed data were analysed with an independent T-test, as the Shapiro-Wilks test indicated no significant difference from a normal distribution (EG: p=0.46, CG: p=0.43, Appendix 8.2) and equal variances could be assumed, as Levene's test was not significant (p=0.48).

they tended to rate their overall recovery (SIS-9) as moderate. Noteworthy were the problems expressed in the hand function domain (SIS-7), with most participants in both groups indicating that they were unable to perform any of the activities at all. Appendix 4.2 shows that all the SIS data were normally distributed, except those pertaining to hand-function (SIS-7; EG: $p=0.01$, CG: $p<0.01$), with data being negatively skewed. There was a trend for the strength scores (SIS-1) in the EG to be abnormally distributed ($p=0.08$). Mann-Whitney U tests showed that were no significant differences in any of the SIS domains between the two groups at baseline ($0.14 \leq p \leq 0.97$).

Appendix 4.10 list the specific ADLs which participants needed assistance with. Overall, most of them were independent in personal hygiene, transfers, ambulation (with or without a stick), stair climbing and visiting the toilet, while minimal assistance tended to be required with cutting up food, donning and doffing socks, shoes, bras as well as fastening zips and buttons.

In summary, baseline data indicated that both groups had severe impairments and activity limitations involving their affected upper limb. Interestingly, although difficulties were reported in terms of ADL, this domain appeared to be less affected than hand function in both groups. Other domains, including cognition, emotion, communication and general mobility, had been less seriously affected, well recovered or were adequately compensated for. Overall, in clinical terms - but apart from gender - the groups were well matched.

4.3.2 OCCUPATIONAL PERFORMANCE ISSUES

Table 4.3 lists the number and nature of the issues, related to participants' productivity, leisure and self-care, which emerged from the Canadian Occupational Performance Measure (COPM). Using the decision tree in fig. 3.7, upper limb-related issues were selected from all other issues that were raised. The latter were used for descriptive purposes only, while the former were also used in the analysis. Both groups identified the same number of issues (n=28), but more UL-related issues were identified in the EG (n=19) than in the CG (n=13). Most issues appeared to belong to the self-care domain, whilst a smaller proportion was related

to leisure. Interestingly, many of the non-UL related issues signalled participation restrictions, which reflected the data on the corresponding SIS domain (SIS-8, Table 4.2.[b]).

Self-rated occupational performance involving the upper limb, expressed on the performance dimension (COPM-P), yielded low marks in both groups. Out of a maximum of 10 points, the EG scored a median of 3.0 points (range 2.0 to 4.0 points) and the CG scored a median of 3.0 points (range 1.0 to 8.0 points). In terms of their satisfaction with performance (COPM-S), the EG: scored a median of 3.0 points (range 1.0 to 4.5 points) and the CG rated their score at a median of 2.0 points (range 1.0 to 8.0 points). All COPM baseline data were normally distributed, except for the COPM-S data in the CG ($p=0.03$), which were positively skewed. There were no significant differences between the two groups at baseline, either in terms of the COPM-P ($U= 23.5$, $p=0.92$), or the COPM-S ($U=22.5$, $p=0.81$).

Table 4.3
Issues identified through the Canadian Occupational Performance Measure at baseline.
EG: Experimental Group, CG: Control Group, UL: upper limb.
Issues were articulated by each participant and noted by the therapist.

Issues Raised	EG (n=7)	CG (n=7)
Total number of issues	28	28
Number of UL issues	19	13
Number of non-UL issues	9	15
UL issues	▪ unable to put on AFO ▪ difficulty getting shoes on and off ▪ unable to connect catheter bags up at night ▪ needing help to get washed ▪ unable to eat using two hands ▪ difficulty opening packaging/ jars ▪ unable to do much cooking ▪ unable to make snacks ▪ unable to cook or make a sandwich ▪ unable to butter toast ▪ needing help to cut up food ▪ difficulty keeping pages of a book open when reading ▪ difficulty putting paper into envelopes ▪ difficulty making notes on the telephone ▪ difficulty writing letters ▪ unable to use the computer ▪ unable to use ladders ▪ unable to do woodwork ▪ unable to do even small painting/ decorating jobs	▪ arm becoming tense when walking outside ▪ arm tightening during ironing ▪ inability to peg clothes out ▪ unable to do any exercise ▪ difficulty turning embroidery over ▪ unable to peel vegetables, using two hands ▪ unable to use two hands to eat ▪ difficulty chopping up food ▪ unable to do any cooking ▪ difficulty opening the fridge door ▪ unable to do small jobs around the house ▪ unable to clean windows due to pain ▪ unable to do any gardening
Non-UL issues	▪ difficulty with tasks in standing ▪ falls caused by catching toes when walking/ running ▪ difficulty checking out new pubs/ areas ▪ difficulty with going on holiday ▪ unable to use the bus or metro independently ▪ unable to cross roads ▪ difficulties with computer skills ▪ unable to find work ▪ difficulty knowing the time/ day	▪ unable to clear secretions out of mouth ▪ difficulty talking for long/ swallowing ▪ missing bits when shaving ▪ unable to use the telephone ▪ difficulty seeing things on the right ▪ unable to go swimming due to facilities ▪ unable to bathe without help ▪ difficulty walking downstairs safely without banister ▪ falling in garden ▪ unable to go watch football when it is windy ▪ unable to drive ▪ tired after 2 hours at work ▪ difficulty with memory at work ▪ difficulty shopping for clothes ▪ difficulty going on holiday

4.4 BOTULINUM TOXIN TYPE-A TREATMENT AT START OF STUDY

Table 4.4[a] provides details of BTX-A treatment for each group, while more detailed information for each participant can be found in table 4.4[b]. Most participants were injected with Dysport® (Ipsen Ltd. Slough, UK): the mean total injected dosage being 318 MU (SD=192) in the EG, compared with 402 mU (SD= 97) in the CG. As the distribution of data was significantly different from normal in the CG, a Mann Whitney test was used, which indicated that the dosage of BTX-A was not significantly different between the two groups at the start of the study (U=17.5, p=0.41). In both groups, the most frequently injected muscles were the forearm flexors. Otherwise, there was considerable variation in terms of injection site and dosage within both groups. Infrequent were injections in the m. triceps brachii (n=1 in EG), the m. pectoralis major (n=1 in CG) and the intrinsic muscles of the hand (n=1 in EG). From table 4.4[b] it can be seen that, in the EG, only two participants (P03 and P06) received BTX-A in their elbow flexors. In the CG, this proportion was six out of seven, with P12 being the exception. Given this small set of data, the planned sub-analysis, set out in section 3.6.3 was omitted. Instead, the spasticity analysis to be reported below was carried out on the cohort as a whole.

Table 4.4[a]
Botulinum toxin –type A treatment at start of study
EG: Experimental Group. CG: Control Group. Type of toxin: "D": Dysport®[3], "A": Allergan®[4]. MU: mouse units. Injection sites: the frequency indicates the number of participants receiving an injection into a specific muscle (group). Dosage: * Based on Odergren (1998), the dosage for the Allergan product (Botox®) was converted to dosage for the Ipsen product (Dysport®) using the following conversion: Dysport®: Botox® = 3.1: 1.

Botulinum Toxin treatment	EG (n=7)	CG (n=7)
Type of toxin (frequency)		
Dysport®	n=7	n=6
Botox®	n=0	n=1
Mean Total Dosage Dysport®(MU)*	318	402
SD	192	97
Min	75	200
Max	600	500

[3] Dysport®, Ipsen Ltd., Slough, UK
[4] Botox®, Allergan Ltd, High Wycombe, UK

Table 4.4[b]

Botulinum toxin treatment at start of study: details for each participant

EG: Experimental Group. CG: Control Group. BTX:Type of toxin: "D": Dysport®, "A": Allergan®. Injection sites: PM: m. pectoralis major, BB: m. biceps brachii, TB: m. triceps brachii, BR: m. brachioradialis, PT: m. pronator teres, FDS: m. flexor digitorum superficialis, FDP: m. flexor digitorum profundus, AP: m. adductor pollicis, IHM: intrinsic hand muscles. N: number of participants injected in a particular muscle (group). Dosage: * The Allergan dosage was converted to Dysport units using the following conversion: Dysport®: Botox® = 3.1: 1 (Odergren, 1998).

EG Participant ID	**BTX**	**PM**	**BB**	**TB**	**BR**	**PT**	**FDS & FDP**	**AP**	**IHM**	***Total***	***Total Converted***
3	D	0	200	0	100	0	3x100	0	0	*600*	*600*
6	D	0	100	0	150	0	2x150	0	0	*400*	*400*
7	D	0	0	200	0	0	3x100	0	0	*500*	*500*
10	D	0	150	0	0	0	2x75	0	0	*300*	*300*
11	D	0	0	0	0	0	3x67	0	0	*200*	*200*
13	D	0	0	0	0	0	75	0	0	*75*	*75*
15	D	0	0	0	0	0	0	0	3*50	*150*	*150*
Mean (SD)		**0 (0)**	**60 (89)**	**40 (89)**	**20 (45)**	**0 (0)**	**221 (95)**	**0 (0)**	**21 (57)**	**318 (192)**	**318 (192)**
Min		**0**	**0**	**0**	**0**	**0**	**75**	**0**	**0**	**75**	**75**
Max		**0**	**200**	**200**	**100**	**0**	**300**	**0**	**150**	**600**	**600**
N		**0**	**3**	**1**	**2**	**0**	**6**	**0**	**1**		
CG Participant ID	**BTX**	**PM**	**BB**	**TB**	**BR**	**PT**	**FDS & FDP**	**AP**	**IHM**	***Total***	***Total Converted***
2	D	0	250	0	150	0	0	0	0	*400*	*400*
4	A	40	40	0	0	0	2x30	10	0	*150**	*465*
5	D	0	100	0	0	0	2x125	50	0	*400*	*400*
8	D	0	150	0	150	0	2x75	0	0	*450*	*450*
9	D	0	200	0	100	0	2x100	0	0	*500*	*500*
12	D	0	0	0	0	0	2x100	0	0	*200*	*200*
14	D	0	100	0	100	0	2x100	0	0	*400*	*400*
Mean (SD)		**6 (15)**	**120 (87)**	**0 (0)**	**71 (70)**	**0 (0)**	**151 (89)**	**9 (19)**	**0 (0)**		***402 (97)***
Min		**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**		***200***
Max		**40**	**250**	**0**	**150**	**0**	**250**	**50**	**0**		***500***
N		**1**	**6**	**0**	**4**	**0**	**6**	**2**	**0**		

4.5 DROP-OUTS, ADVERSE EVENTS AND ATTENDANCE

4.5.1 DROP-OUTS

During the first week of the intervention programme, the therapist observed increasing anxiety, fatigue and concentration difficulties in two participants in the EG. Following extensive consultation between the therapist, her line manager, the participants themselves and their spouses, it was decided it would be in the best interest of the participants to withdraw from the trial. Participant P10 appeared to experience anxiety over his transport arrangements to and from the clinic, which were detrimental to his ability to concentrate during the therapy sessions. With regards to participant P15, the therapist noted concentration difficulties at the initial assessment, which increased over the following days. The participant's spouse revealed that the participant had been generally unwell prior to study enrolment – which, regrettably, had not been reported during the eligibility screening. The therapist advised the couple to visit their GP without delay.

Baseline data for participants P10 and P15 are included in Tables 8.2[a] and 8.2[b] but these were not used for the analysis of the treatment effects. An overview of baseline data from the remaining five participants in the EG who completed the programme is presented in Appendix 4.3 and these data were used in the analysis.

There were no drop-outs in the CG.

All participants received the intended form of intervention. In all participants, the primary outcome measures were analysed.

4.5.2 ADVERSE EVENTS

An overview of the adverse events in the study groups, including participants P10 and P15, is provided in table 4.5. There were no serious adverse events related to the therapy programme or the BTX-A. However, three serious, non-therapy related events occurred while two participants (both in the EG) engaged in DIY activities at home. Participant P11 sustained a bilateral clavicula fracture as he tripped up and fell down the stairs while assisting a friend moving a large piece of furniture. As this took place during the last phase of the study, he was unable to take part in the final

assessment. Participant P13 experienced severe neck and arm pain after carrying out a DIY job in the last phase of the study period, but was able to take part in the final assessment, which took place two weeks after the date that had been scheduled originally. Additionally, one serious, non-treatment related event occurred when participant P05 (CG) collapsed during an unusually hot summer's day when visiting friends.

The two groups reported the same number of adverse events, most commonly transient UL pain and fatigue.

Table 4.5

Adverse events during the study period

Overview of adverse events for each of the two study groups.
EG: Experimental Group, CG: Control Group, UL: upper limb, DVT: deep venous thrombosis

Adverse events	EG (n=7)	CG (n=7)
Overall number of adverse events	17	17
Therapy-related events (frequency)		
Fatigue	5	5
Anxiety and problems with concentration	2	0
Extensor spasms	1	0
UL tightness	0	1
Transient upper limb pain	4	3
Transient neck pain	0	1
Reduction in pinch force	1	0
Hyperesthesia in hand	0	1
Non-therapy-related events (frequency)		
Leg pain, possible DVT	1	0
Foot infection	0	1
Common cold	0	2
Menstrual pain	0	1
Bruised hand	0	1
Bladder incontinence	1	0
Collapse due to heat	0	1
Upper limb fracture (bilateral)	1	0
Pain, weakness in neck and affected UL	1	0

4.5.3 ATTENDANCE

Table 4.6 details the levels of attendance for each group, after participants P10 and P15 had been removed from the dataset. Therapy attendance was high in both groups and non-attendance was caused by reasons beyond control of the participants.

Table 4.6
Attendance over the 3-week therapy period following treatment with botulinum toxin type-A
EG: Experimental Group, CG: Control Group. The frequency refers to the number of occasions a particular event took place.

Attendance	EG (n=5)	CG (n=7)
Overall attendance (%)	92%	89%
Participant-related reasons (frequency)		
Unwell	1	3
Unexpected social commitments	1	3
Work commitments	0	1
Other reasons (frequency)		
Complications with logistics	4	5

4.6 BETWEEN-GROUP DIFFERENCES IN CHANGES OVER TIME

Given the restricted size of the dataset, several options were considered for the analysis. Had the sample size turned out as planned (i.e. n=46 for the entire study), the preferred method would have involved mixed models (Brown and Prescott, 1999), which provide advanced techniques for investigating between- and within-group changes over repeated assessments. However, given the very small sample size and non-normal distribution of some of the primary outcome measures (Appendix 4.2), this was not thought to be a viable option. Using more conventional statistics was also considered. The intention had been to stratify the data according to baseline levels, but again the sample size did not permit this. Had all data been of interval or ratio level and normally distributed, an analysis of covariance would have been considered, but since the primary outcome measures (i.e. ARAT, COPM) were ordinal level variables and their distributions were significantly different from normal, this possibility had to be ruled out also. After careful consideration, repeated Mann-Whitney U tests were chosen for all data, the main purpose being to explore between-group differences in change over selected periods of time. In the light of the sample size, *exact* p-values were used (Kinnear and Gray, 2004). In order to limit the experiment-wise error rate associated with repeated measures (Field, 2000), the Bonferroni correction was applied, dividing α (originally set at 0.05) by 3. This yielded a critical p-value of 0.017. All tests were two-tailed.

It can probably not be emphasised enough that these tests were carried out solely to enable a tentative exploration of the data. The results, to be presented in the following sections, therefore need to be interpreted with due caution.

In the ensuing sections, the findings will be presented as follows: for each of the study phases (i.e. week 0-4, week 0-7 and week 0-13), changes within the EG and the CG will be described, followed by an analysis of the difference in change between the two groups. In order to provide a uniform appearance, all data will be illustrated as box plots, as the majority of outcome measures were of an ordinal level.

4.6.1 BASELINE TO AFTER TREATMENT (WEEK 0 TO WEEK 4)

Table 4.7 shows a summary of the changes that took place between baseline (Week 0) and the end of the therapy programme (Week 4). Appendix 4.4 shows the outcomes at Week 4 and Appendix 4.5 indicates the changes from Week 0 to Week 4 at the level of individual participants.

Table 4.7
Overview of the changes in outcome measures from Week 0 to Week 4 for the Experimental Group (EG: n=5) and the Control Group (CG: n=7).
EG: experimental group, CG: control group. ARAT: Action Research Arm Test, COPM-P: Canadian Occupational Performance Measure-Performance, COPM-S: Canadian Occupational Performance Measure-Satisfaction, EMG: EMG of the elbow flexors of the affected arm during the Ashworth test, RTPM: resistance to passive movement during the Ashworth test, AS: Ashworth Scale, GF Aff: Grip force of the affected hand (mean and SD of three trials), SIS: Stroke Impact Scale.
If ratio-level data were normally distributed, their measure of central tendency was expressed in means instead of medians.

Outcome	EG Median or Mean change (min-max)	CG Median or Mean change (min-max)	Difference between EG-CG: level of significance
ARAT (score) (median total score)	**2** (-2 – 9)	**0** (-2 – 1)	ns
COPM-P (score) (median (median score))	**3.0** (1.5 – 5.0)	**0.5** (-2 – 3.5)	ns
COPM-S (score) (median (median score))	**2.5** (1.5 – 5.0)	**2.0** (-6.0 – 5.5)	ns
EMG (mV) (mean)	**-0.011** (-0.058 – 0.096)	**0.000** (-0.063 – 0.052)	ns
RTPM (N/deg) (mean)	0.04 -0.35 – 0.36	-0.08 -0.40 – 0.11	ns
Ashworth (score) (median)	**-1** (-1 – 1)	**-1** (-1 – 0)	ns
Grip Force affected hand (N) (mean)	**2.7** (-13.8 – 14.7)	**-7.5** (-52.2 – 16.3)	ns
SIS-5 ADL (%) (median)	**7.5** (-2.5 – 12.5)	**5.0** (-15.0 – 7.5)	ns
SIS-7 Hand function (%) (median)	**25.0** (0.0 – 30.0)	**0.0** (-10.0 – 0.0)	*
SIS-8 Participation (%) (median)	**0.0** (-25.0 – 40.6)	**-3.1** (-15.7 – 6.3)	ns

ns: non-significant; *: significant at $p<0.05$; **: significant at $p< 0.017$.

ARAT: from week 0 to week 4

In the EG, the median change over this period was 2 points (range -2 to 9 points), with four of the five participants showing a positive change, although the performance of one participant (P07) deteriorated by 2 points.

In the CG, the median ARAT change was 0 points (range -2 to 1 points), with a decrease of 2 points in one participant (P04).

The difference between the EG and CG in terms of change in ARAT over this period was not significant (U=8.00, p=0.13). Figure 4.1 shows that changes in the EG and CG partially overlap, but that a number of more substantial improvements were seen in the EG than in the CG, whilst changes in the CG were marginal.

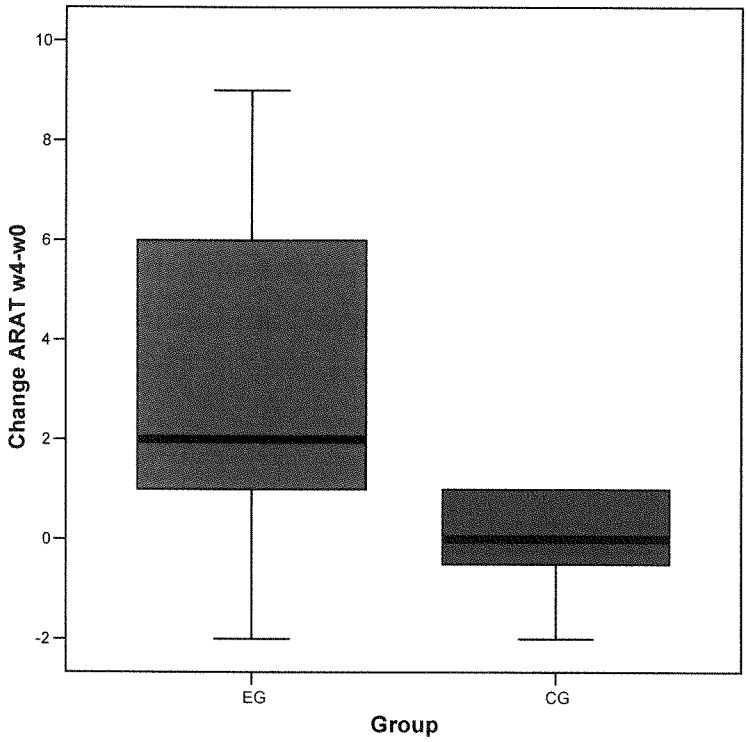


Figure 4.1
Median changes in total ARAT scores from week 0 to week 4
EG: Experimental Group, CG: Control Group.

COPM: from week 0 to week 4

In terms of perceived performance on self-selected issues, all five participants in the EG indicated an improvement on the COPM-P (median change 3.0 points, range 1.5 to 5.0 points). In terms of satisfaction with their performance, the median COPM-S

change for the EG was 2.5 points, (range 1.5 to 5.0 points) again with all participants improving.

In the CG, the median COPM-P change was 0.5 points (range -2.0 to 3.5 points). Four of the seven participants showed a positive change, but results in the remaining three varied. On the COPM-S, the median change was 2.0 points, but the range (-6.0 to 5.5 points) indicated again considerable variation.

Figure 4.2 illustrates that, over this initial study period, changes in both COPM dimensions were positive in the EG, in contrast to the CG, where the results were mixed. The change in the COPM-P was more positive in the EG than in the CG, but this was not statistically significant (U=6.00, p=0.06). The difference between the two groups in terms of changes in the COPM-S was also not significant (U=14.5, p=0.67).

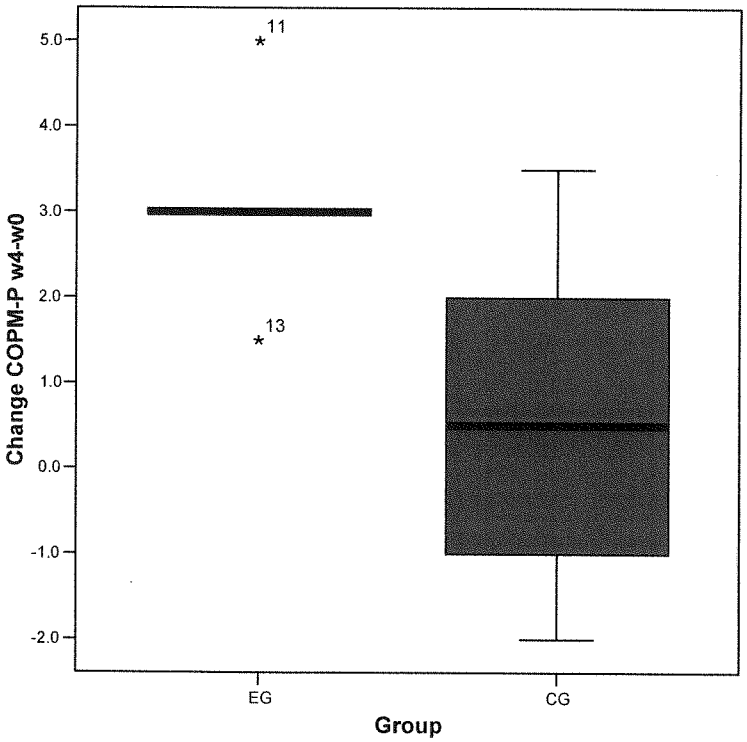


Figure 4.2a
Median changes in Canadian Occupational Measure of Performance (COPM-P) scores from week 0 to week 4
COPM-Performance
EG: Experimental Group, CG: Control Group.

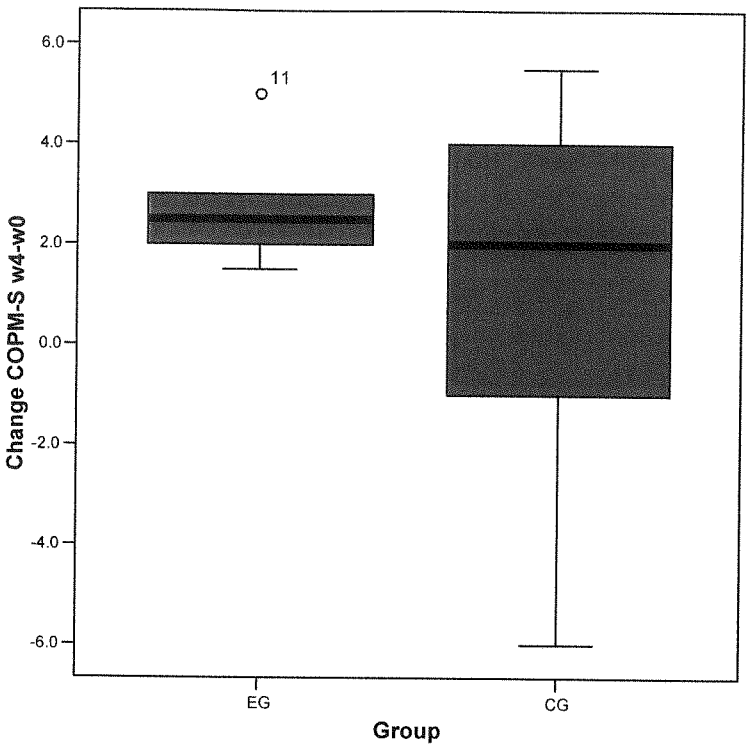


Figure 4.2b
Median changes in Canadian Occupational Measure of Performance (COPM-S) scores from week 0 to week 4
COPM-Satisfaction
EG: Experimental Group, CG: Control Group.

EMG: from week 0 to week 4

In the EG, the median change in elbow flexor activity was minimal (-0.011 mV, range -0.058 to 0.096 mV). Figure 4.3 shows one outlier (Participant P07), the only case in the EG where EMG increased following the intervention. In the CG, results were more mixed (mean change -0.000 mV, range -0.063 to 0.052 mV).

The difference in change in EMG between the two groups was not significant (U=13.0, p=0.53) over this study period.

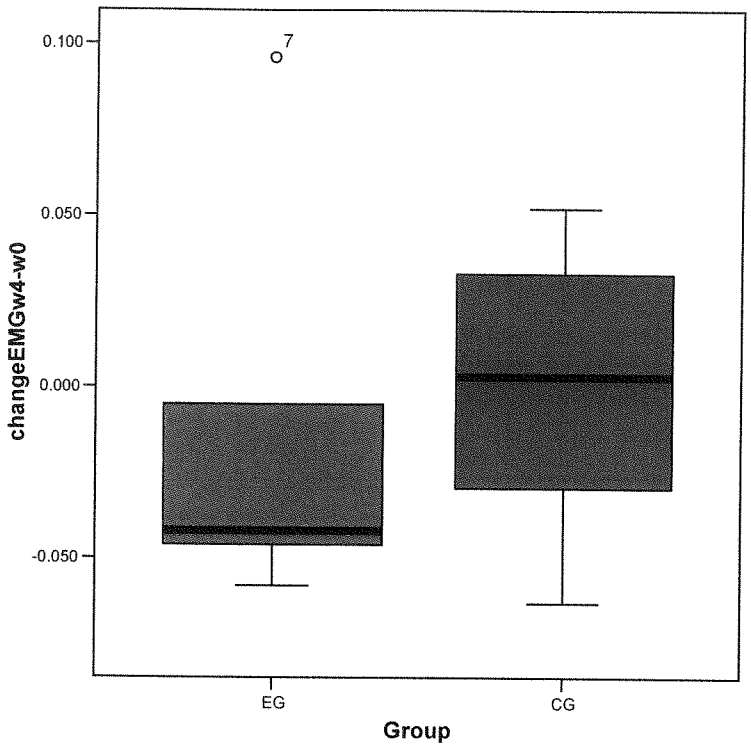


Figure 4.3
Median changes in elbow flexor activity (EMG, mV) from week 0 to week 4
EG: Experimental Group, CG: Control Group.

RTPM: from week 0 to week 4

In the EG, RTPM increased (mean change 0.04 N/deg, range -0.35 to 0.36 N/deg), with four participants showing a rise; particularly participant P06. Interestingly, given the EMG results described above, participant P07 was the only individual in whom RTPM decreased. In the CG, RTPM generally decreased (mean change: -0.08 N/deg, range -0.40 to 0.11 N/deg), with an improvement in five out of seven participants.

The difference in change in RTPM between the two groups over this study phase was not significant (U=12.0, p= 0.43), fig. 4.4.

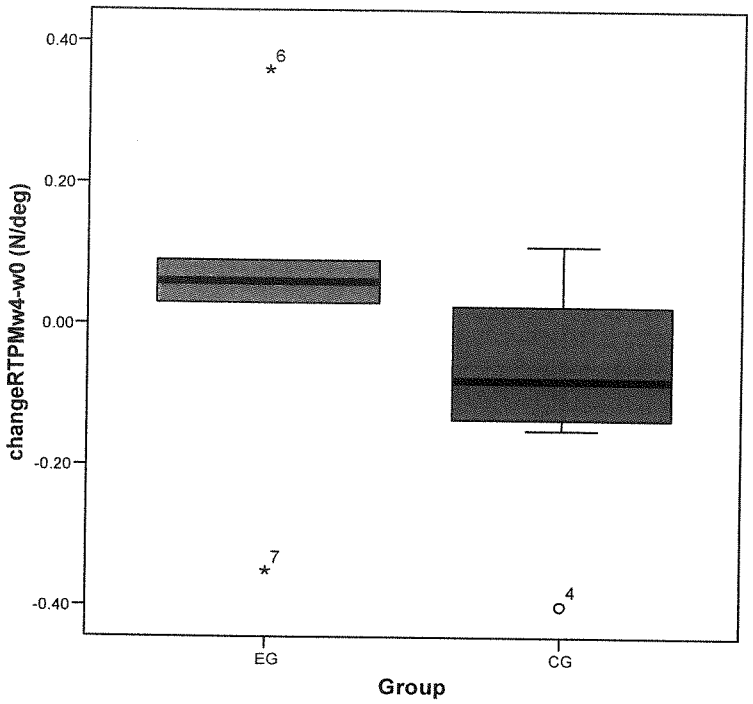


Figure 4.4
Median changes in Resistance to Passive Movement (N/deg): week 0 to week 4
EG: Experimental Group, CG: Control Group

Ashworth Scale: from week 0 to week 4

In the EG, the median change in AS was -1 point (range -1 to 1 point), signalling a reduction in RTPM. The AS reduced by 1 point in three participants, did not change in one (P13), while it increased by 1 point in another (P11).

In the CG, median change in AS was also –1 point (range -1 to 0 point), with four participants showing a 1-point reduction, whilst no change was noted for the remaining three participants. The difference in change in AS between the two groups was not significant (U=16.5, p= 1.00), fig. 4.5.

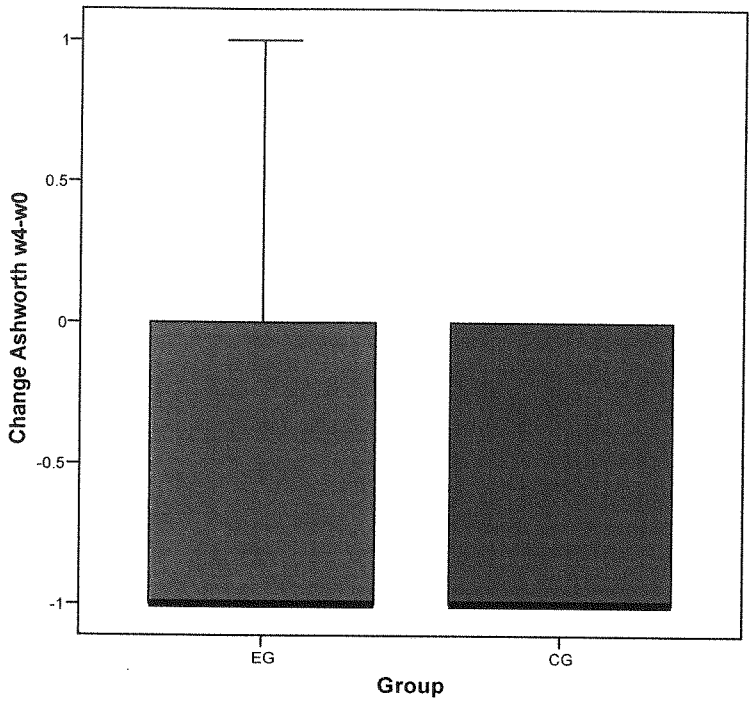


Figure 4.5
Median changes in Ashworth scale for the elbow joint from week 0 to week 4
EG: Experimental Group, CG: Control Group

Grip Force: from week 0 to week 4

In the EG, the average change in grip force of the affected hand was negligible (mean 2.7 N, SD 11.4). In the CG, the average change in grip force was –7.5 N (SD 25.6). Considerable inter-subject variation was apparent (Appendix 4.5).

The difference in change in GF of the affected hand between the two groups was not significant (U=15.0, p=0.72), fig. 4.6.

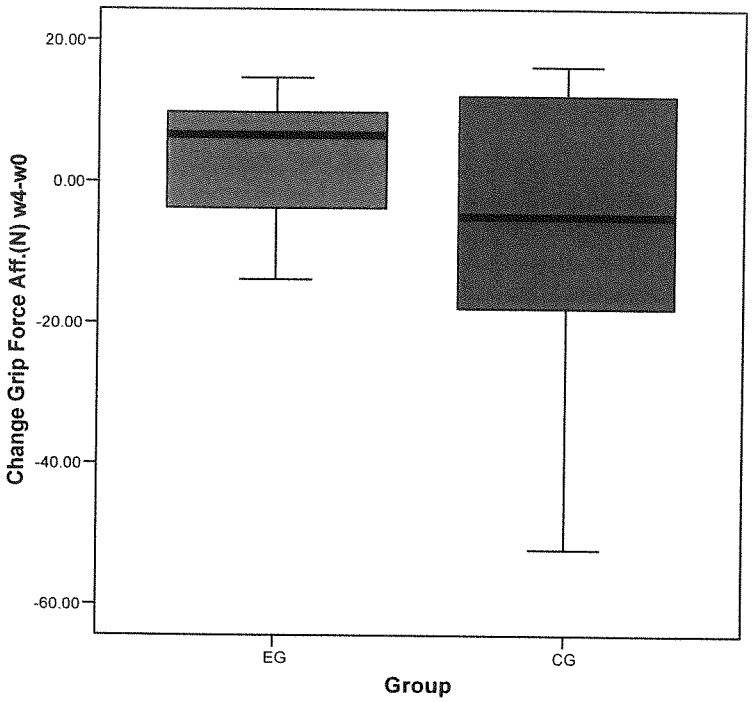


Figure 4.6
Median changes in Grip Force (N) of the affected hand from week 0 to week 4
EG: Experimental Group, CG: Control Group

Stroke Impact Scale: from week 0 to week 4

All five participants in the EG and five out of seven participants in the CG returned their completed SIS questionnaire.

In terms of ADL (SIS-5), the EG noted a small improvement (median change 7.5%, range -2.5 to 12.5%), while the median change in the CG was 5.0% (range -15.0 to 7.5%). The difference between the two groups over the period from baseline to week four was not significant (U=8.00, p=0.40). Figure 4.7[a] illustrates that there was considerable overlap between the two groups in terms of ADL, although some greater improvements were noted for the EG.

With regards to self-rated hand function (SIS-7), the median improvement in the EG was 25% (range 0 to 30%), with three of the five participants documenting an increase of 25% or more, whilst little or no change was noted for the other two participants (P06 and P13). In the CG, median SIS-7 did not improve (median change 0%, range -10 to 0%). Figure 4.7[b] illustrates that there were greater improvements in self-reported hand function in the EG compared to the CG, but this difference did not reach the critical p-value (U=2.00, p=0.04).

In terms of participation (SIS-8), the median change in the EG was 0% (range -25 to 40.6%), showing equivocal results with considerable inter-subject variation. In the CG, the median change was -3.1% (range -15.7 to 6.3%), also with mixed results, albeit of a smaller range than those in the EG (Fig. 4.7 [b]).

The difference in change in participation between the two groups was not statistically significant over this study phase (U=11.0, p=0.84).

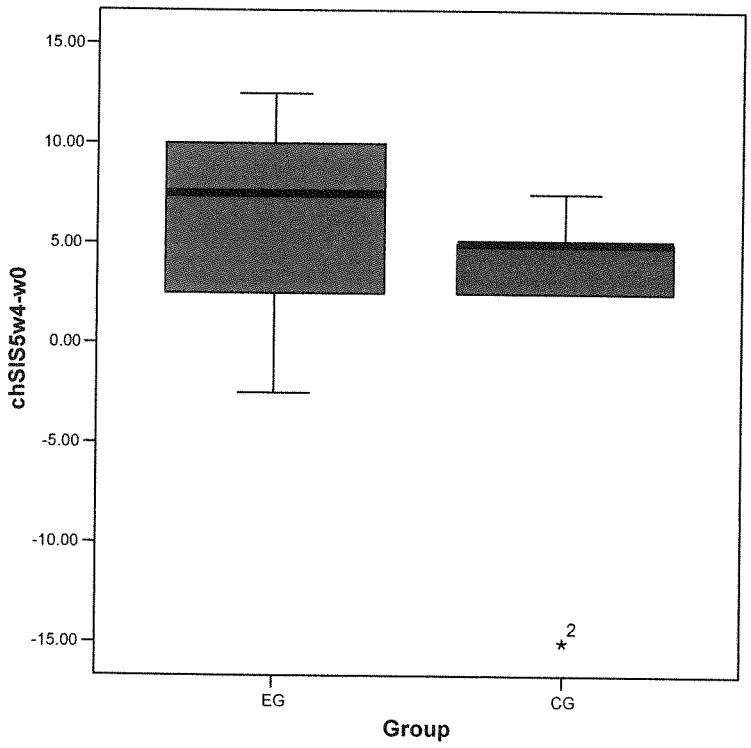
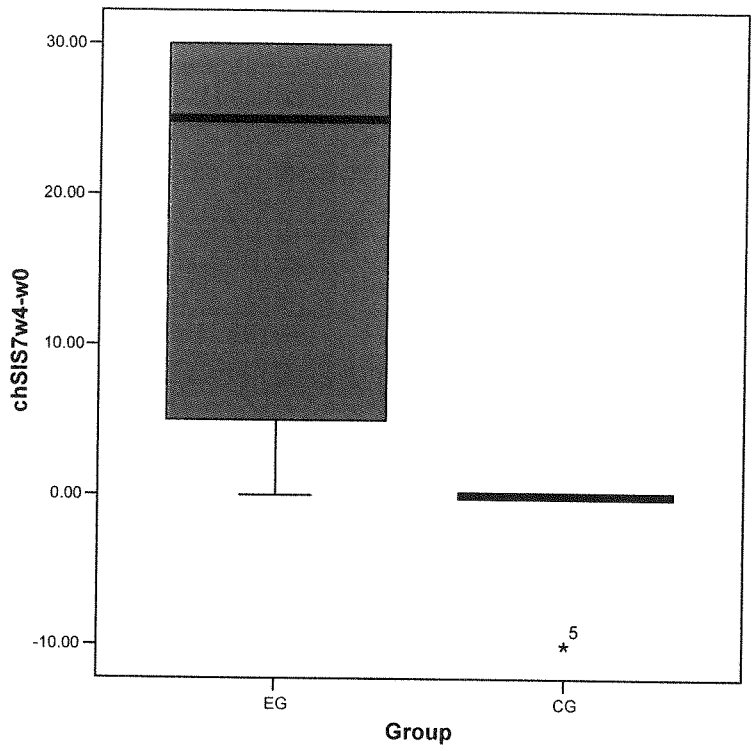


Figure 4.7[a]
Median changes in Stroke Impact Scale (SIS) domain scores (%) from week 0 to week 4
ADL (SIS-5)



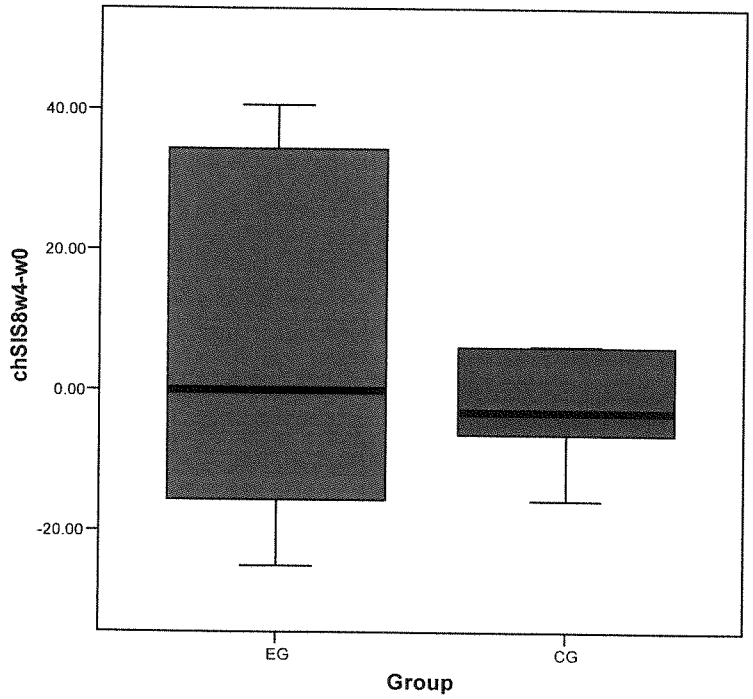


Figure 4.7[b]
Median changes in Stroke Impact Scale (SIS) domain scores (%) from week 0 to week 4
Top: Hand Function (SIS-7); bottom: Participation (SIS-8).
EG: Experimental Group, CG: Control Group

Summary of differential changes between EG and CG (Week 0 to Week 4)

In summary, the EG showed an improvement in self-rated performance of self-selected goals (COPM-P) with a median change of 3 points (range 1.5 to 5.0 points), compared with 0.5 points (range -2.0 to 3.5 points) in the CG (p=0.06). Additionally, self-reported hand function (SIS-7) improved in the EG (median improvement 25%, range 0.0 to 30.0%) compared with the CG, where the median change was 0.0%, ranging from -10.0 to 0.0% (p=0.04). However, none of these differential changes reached statistical significance. There were no other statistically significant differences between the EG and the CG in terms of any of the other outcome measures from before to immediately after the therapy programme.

4.6.2 BASELINE TO MID-WAY (WEEK 0 TO WEEK 7)

Data pertaining to changes over the period from baseline to midway through the study period are presented in table 4.8. As stated in the previous section, participant P07 was unable to take part in the Week 7 assessment due to illness. No statistical tests were applied to the SIS data, because of the limited response. Data pertaining to individual participants over this period can be found in Appendix 4.7.

Table 4.8
Overview of the changes in outcome measures from Week 0 to Week 7 for the Experimental Group (EG: n=4) and the Control Group (CG: n=7).
EG: experimental group, CG: control group. ARAT: Action Research Arm Test, EMG: EMG of the elbow flexors of the affected arm during the Ashworth test, RTPM: resistance to passive movement during the Ashworth test, AS: Ashworth Scale, GF Aff: Grip force of the affected hand (mean and SD of three trials), SIS: Stroke Impact Scale.
If ratio-level data were normally distributed, their measure of central tendency was expressed in means instead of medians.

Outcome	EG Median or Mean change (min-max)	CG Median or Mean change (min-max)	Difference between EG-CG: level of significance
ARAT (score) (median total score)	**4** (1 – 8)	**-1** (-3 – 0)	**
EMG (mV) (mean)	**-0.030** (-0.061 – 0.003)	**-0.002** (-0.063 – 0.078)	ns
RTPM (N/deg) (mean)	**0.11** (-0.17 – 0.28)	**-0.07** (-0.56 – 0.40)	ns
Ashworth (score) (median)	**-0.5** (-1 – 1)	**0** (-2 – 0)	ns
Grip Force affected hand (N) (mean)	**2.3** (-10.6 – 17.9)	**-15.2** (-39.4 – 9.8)	ns
SIS-5 ADL (%) (median)	**5.5** (-5.0 – 15.0)	**-5.0** (-7.5 – 7.5)	NA
SIS-7 Hand function (%) (median)	**15.0** (0.0 – 30.0)	**0.0** (-25.0 – 0.0)	NA
SIS-8 Participation (%) (median)	**3.1** (-12.5 – 12.5)	**-6.2** (-18.8 – 12.5)	NA

ns: non-significant; *: significant at $p<0.05$; **: significant at $p< 0.017$. NA: statistical tests were not applied, as the number of responses was too limited.

ARAT: from week 0 to week 7

In the EG, the median change in ARAT score over this period was 4 points (range 1- to 8 points), with all four participants showing positive changes, although they were minimal (i.e. 1 point) for Participants P03 and P13, but substantial (i.e. 6 and 8 points) for Participants P06 and P11, respectively.

In contrast, the median ARAT change in the CG was –1 point (range -3 to 0 points).

Interestingly, the difference between changes in ARAT scores in the two groups from baseline to three weeks after the end of the therapy programme was statistically significant ($U=0.00$, $p=0.003$), indicating a greater improvement in the EG than the CG over this period. The box plot in fig. 4.8 illustrates these findings and shows that all ARAT changes in the EG were positive and greater than those in the CG.

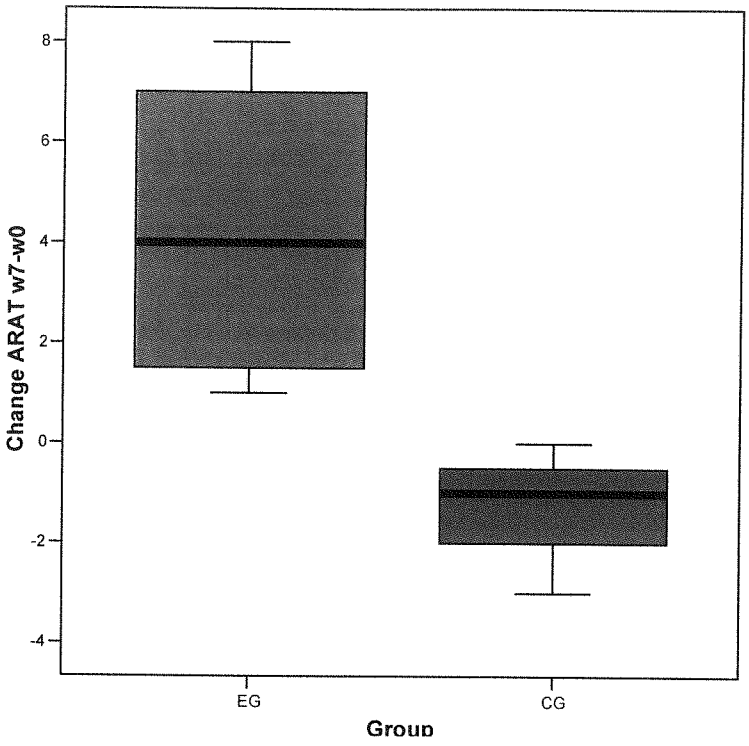


Figure 4.8
Median changes in total ARAT scores from week 0 to week 7
EG: Experimental Group, CG: Control Group

COPM: from week 0 to week 7

The COPM was not assessed at Week 7, as explained in section 3.5.5.

EMG : from week 0 to week 7

Comparing baseline to midway through the study, mean EMG in the EG changed by -0.030 mV (range -0.061 to 0.003 mV). In the CG, average change in EMG was -0.002 mV (range -0.063 to 0.078 mV), with Participant P08 showing the greatest increase. Figure 4.9 shows the boxplot for both groups. The difference between the EG and the CG was not significant (U=10.0, p=0.53).

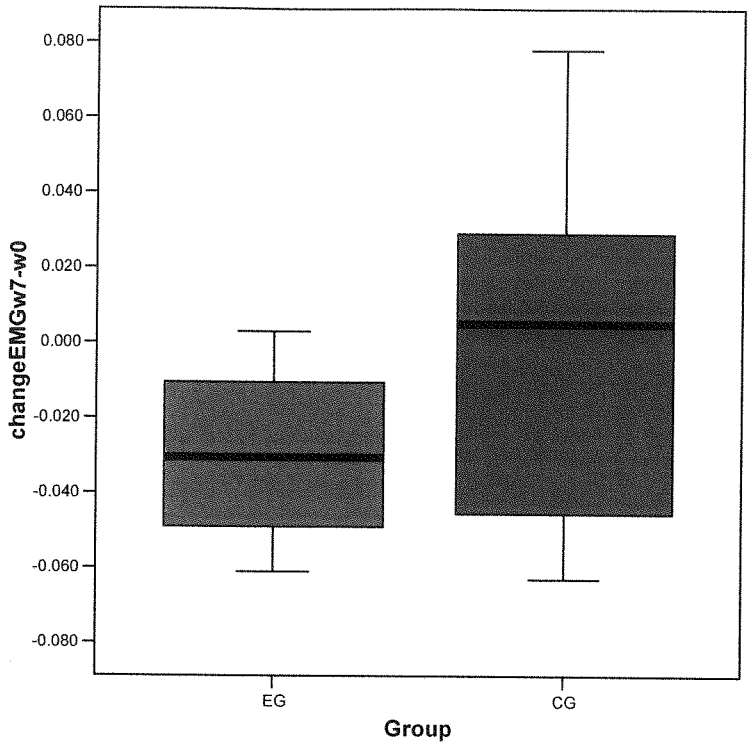


Figure 4.9
Median changes in elbow flexor activity (EMG, mV) from week 0 to week 7
EG: Experimental Group, CG: Control Group

RTPM: from week 0 to week 7

RTPM increased in the EG from baseline to Week 7 (mean change 0.11 N/deg range -0.17 to 0.28 N/deg), with only participant P06 showing an improvement (i.e. a decrease in RTPM). Data from the CG indicated a general decrease in RTPM (mean change -0.07 N/deg, range -0.56 to 0.40 N/deg), with four participants improving and three showing a decline (i.e. an increase in RTPM).

The difference in biomechanically measured RTPM between the two groups was not significant (U=8.0, p=0.32), fig. 4.10.

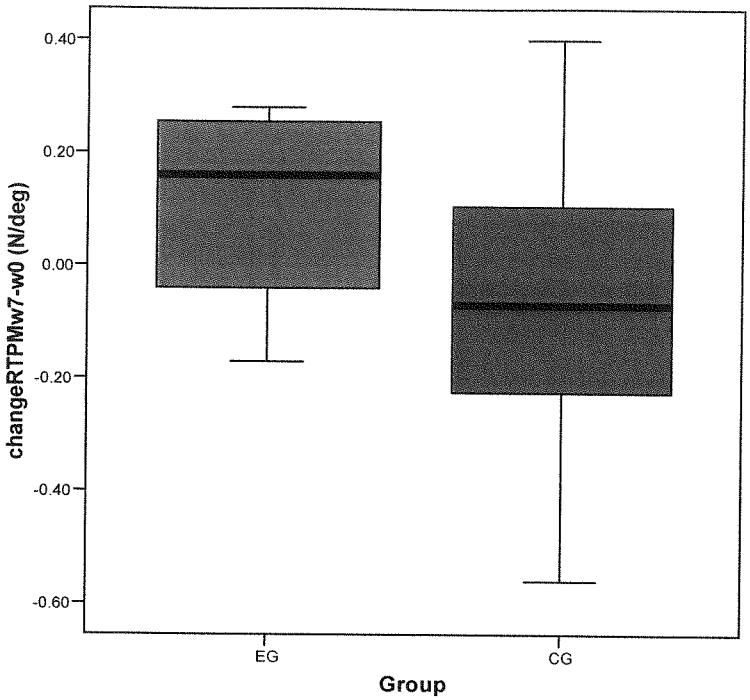


Figure 4.10
Median changes in Resistance to Passive Movement (N/deg): week 0 to week 7
EG: Experimental Group, CG: Control Group

Ashworth Scale: from week 0 to week 7

In the EG, the median change in AS was -0.5 points (range -1 to 1 point), with a decrease in two, no change in one and an increase in another participant (P11).

In the CG, median change in AS was 0 points (range -2 to 0 points), showing a decrease in three and no change in four participants.

The difference in clinically assessed resistance to passive elbow extension between the two groups was not significant (U=12.0, p=0.73), fig. 4.11.

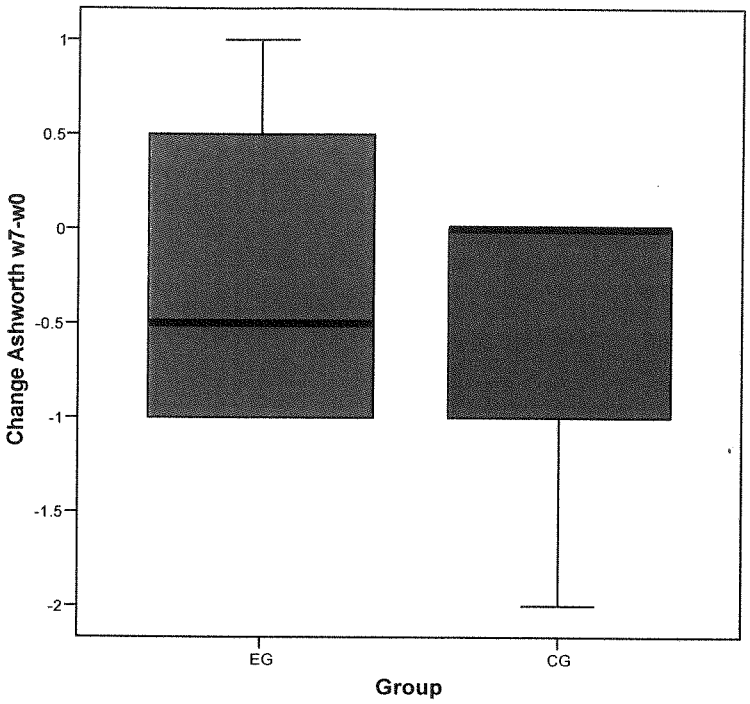


Figure 4.11
Median changes in Ashworth scale for the elbow joint from week 0 to week 7
EG: Experimental Group, CG: Control Group

Grip Force: from week 0 to week 7

In the EG, changes in grip force were very small, with the average change being 2.3 N (SD 13.2). In the CG, grip force showed decline in most participants (mean change -15.2 N, SD 18.0), the largest of which occurred in participant P12 (-39.4N, Appendix 4.7).

The difference in GF of the affected hand between the two groups was not significant (U=5.0, p=0.11), fig. 4.12.

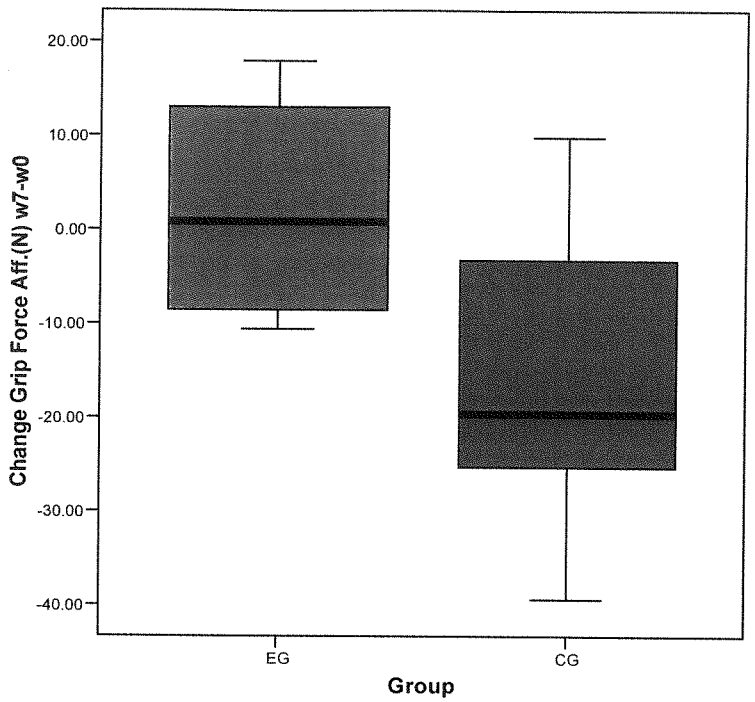


Figure 4.12
Median changes in Grip Force (N) of the affected hand from week 0 to week 7
EG: Experimental Group, CG: Control Group

Stroke Impact Scale: from week 0 to week 7

With missing data from two out of five participants in the EG and two out of seven in the CG, the SIS data pool was severely restricted and therefore all statistical tests, as well as box plots, were omitted.

In terms of ADL (SIS-5), participant P03 in the EG indicated an improvement of 15%, while the small changes in the other two participants (i.e. + 5% and -5%) cancelled each other out. In the CG, no noteworthy changes occurred (median change -5%, range -7.5 to 7.5%).

Hand function (SIS-7) improved notably in participants P03 and P06 in the EG, (i.e. 30 and 15% resp.), but P13 did not indicate any change. In the CG, this variable did not change for the group (median 0%, range -25 to 0%), although a considerable decline was reported by participant P05 (-25%).

Changes in participation (SIS-8) in the EG over this study period were mixed (median change 3.1%, range -12.5 to 12.5%), with a decrease in P03 and an

increase of similar magnitude in P13. In the CG, the median change in SIS-8 was -6.2% (range -18.8 to 12.5%), the improvement in P02 being juxtaposed against the decrease in P05.

Summary of differential changes between EG and CG (Week 0 to Week 7)

Compared to the CG, the EG demonstrated a significant improvement in arm function (ARAT): the median change was 4 points (range 1 to 8 points), versus -1 point (range -3 to 0 points) in the CG (p=0.003). There were no other statistically significant differences between the EG and the CG in terms of any of the other outcome measures over this study phase.

4.6.3 BASELINE TO END OF STUDY (WEEK 0 TO WEEK 13)

Table 4.9 presents an overview of the changes in outcome measures from baseline to the end of the study period. Appendix 4.9 provides corresponding information pertaining to individual participants. As indicated before, due to an unfortunate incident, participant P11 in the EG could not be assessed at week 13.

Table 4.9
Overview of the changes in outcome measures from Week 0 to Week 13 for the Experimental Group (EG: n=4) and the Control Group (CG: n=7).
EG: experimental group, CG: control group. ARAT: Action Research Arm Test, COPM-P: Canadian Occupational Performance Measure-Performance, COPM-S: Canadian Occupational Performance Measure-Satisfaction, EMG: EMG of the elbow flexors of the affected arm during the Ashworth test, RTPM: resistance to passive movement during the Ashworth test, AS: Ashworth Scale, GF Aff: Grip force of the affected hand (mean and SD of three trials), SIS: Stroke Impact Scale.
If ratio-level data were normally distributed, their measure of central tendency was expressed in means instead of medians.

Outcome	EG Median or Mean change (min-max)	CG Median or Mean change (min-max)	Difference between EG-CG: level of significance
ARAT (score) (median total score)	**1.5** (-1 – 7)	**-1** (-2 – 1)	ns
COPM-P (score) (median (median score))	**0.8** (0.0 – 3.0)	**1.0** (-4.0 – 4.5)	ns
COPM-S (score) (median (median score))	**3.5** (1.0 – 4.0)	**2.0** (-6.0 – 4.5)	ns
EMG (mV) (median)	**-0.021** (-0.073 - -0.011)	**0.011** (-0.115 – 0.097)	ns
RTPM (N/deg) (mean)	**0.08** (-0.17 – 0.39)	**-0.13** (-0.40 – 0.12)	ns
Ashworth score (median)	**-0.5** (-1 – 0)	**0** (-1 – 0)	ns
Grip Force affected hand (N) (mean)	**-2.0** (-13.8 – 15.5)	**5.6** (-36.4 – 101.2)	ns
SIS-5 ADL (%) (median)	**11.3** (5.0 – 20.0)	**0.0** (-2.5 – 5.0)	*
SIS-7 Hand function (%) (median)	**2.5** (0.0 – 25.0)	**0.0** (-20.0 – 5.5)	ns
SIS-8 Participation (%) (median)	**3.2** (-12.5 – 6.2)	**9.4** (-21.9 – 40.1)	ns

ns: non-significant; *: significant at $p<0.05$; **: significant at $p< 0.017$.

ARAT: from week 0 to week 13

In the EG, the median ARAT change was small (1.5 points), ranging from -1 to 7 points. The median ARAT change in the CG was -1 point (range -2 to 1 points), indicating only some minor fluctuations.

The difference in ARAT change between the two groups over this period was not significant ($U=7.00$, $p=0.22$). Figure 4.13 illustrates these findings and shows the similarities between the two groups, but also indicates that changes in the EG were generally more positive than those in the CG.

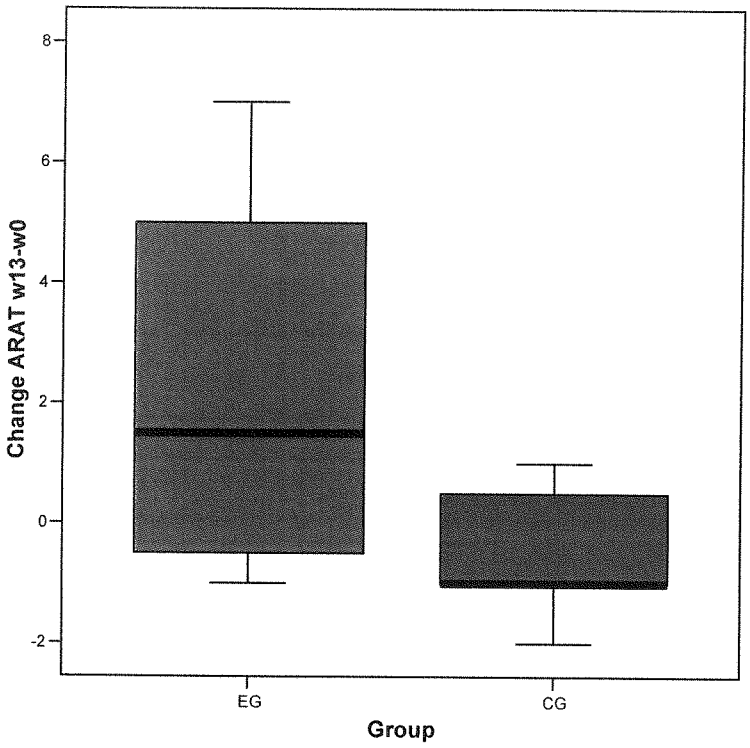


Figure 4.13
Median changes in total ARAT scores from week 0 to week 13
EG: Experimental Group, CG: Control Group.

COPM: from week 0 to week 13

In terms of perceived arm function associated with occupational performance (COPM-P), there was little change in the EG (median 0.8 points, range 0.0 to 3.0 points). Participant P13 improved by three points, but no change was noted in three other cases. Interestingly, in terms of their satisfaction with their performance (COPM-S), all four participants improved (median change 3.5 points, range 1.0 to 4.0 points). Participants P03 and P07, who did not indicate a change on their COPM-P, reported an increase of 4.0 points on the COPM-S.

In the CG, the median change in COPM-P was 1.0 point (range -4.0 to 4.5 points), with five participants improving to varying degrees. More substantial were the changes noted by participants P12 (-4.0 points) and P14 (+4.5 points).

On the COPM-S, the median change was 2.0 points (range -6.0 to 4.5 points), with six participants having improved whilst P12 noted a considerable decline (-6.0 points).

The difference between the two groups with regards to changes in COPM-P scores over this period was not significant (U=13.5, p=0.98) and the same applied to the COPM-S (U=10.0, p=0.47). The box plots in fig. 4.14 clearly depict the similarities between the two groups. The two extreme values on the COPM-P in the CG are participants P14 and P12, the latter of whom also represented the extreme value on the COPM-S in the CG.

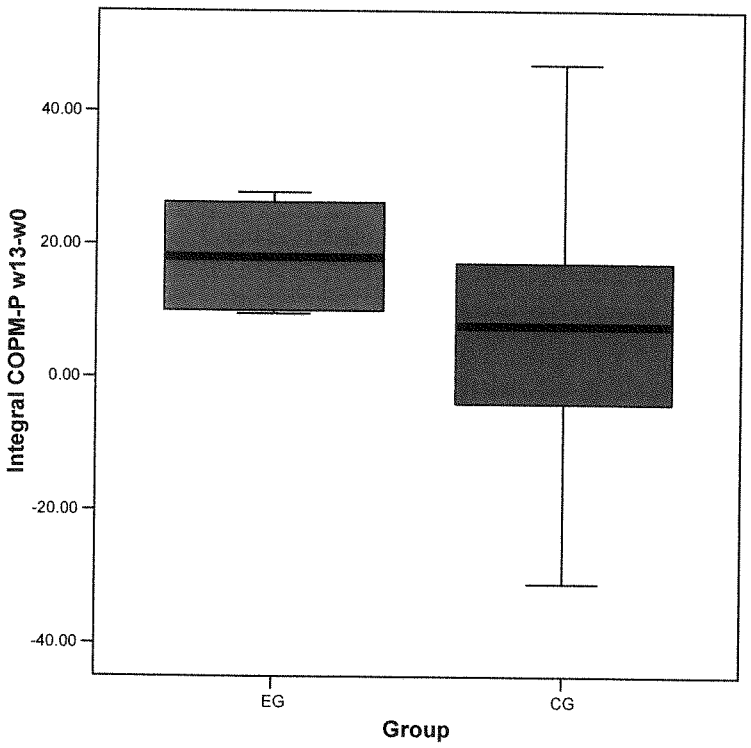


Figure 4.14a
Median changes in Canadian Occupational Measure of Performance (COPM-P) scores from week 0 to week 13
COPM-Performance. EG: Experimental Group, CG: Control Group.

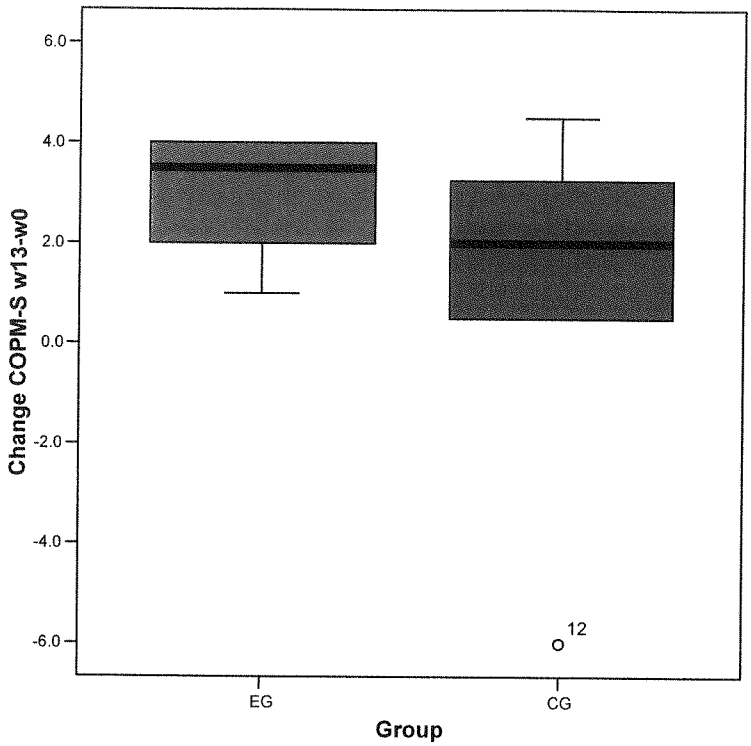


Figure 4.14b
Median changes in Canadian Occupational Measure of Performance (COPM-S) scores from week 0 to week 13
COPM-Satisfaction. EG: Experimental Group, CG: Control Group.

EMG: from week 0 to week 13

The EMG data over this period were not normally distributed in the EG (Appendix 4.2) and therefore measures of central tendency were expressed in medians rather than means.

Compared to baseline, median elbow flexor activity in the EG changed by -0.021 mV (range – 0.073 to -0.011 mV), showing an overall reduction. In the CG, changes in EMG were more varied (median change 0.011 mV, range -0.115 to 0.097 mV), which is illustrated in Figure 4.15.

There was no significant difference between the two groups in terms of changes in elbow flexor activity from baseline to the end of the study (U=10.0, p=0.49).

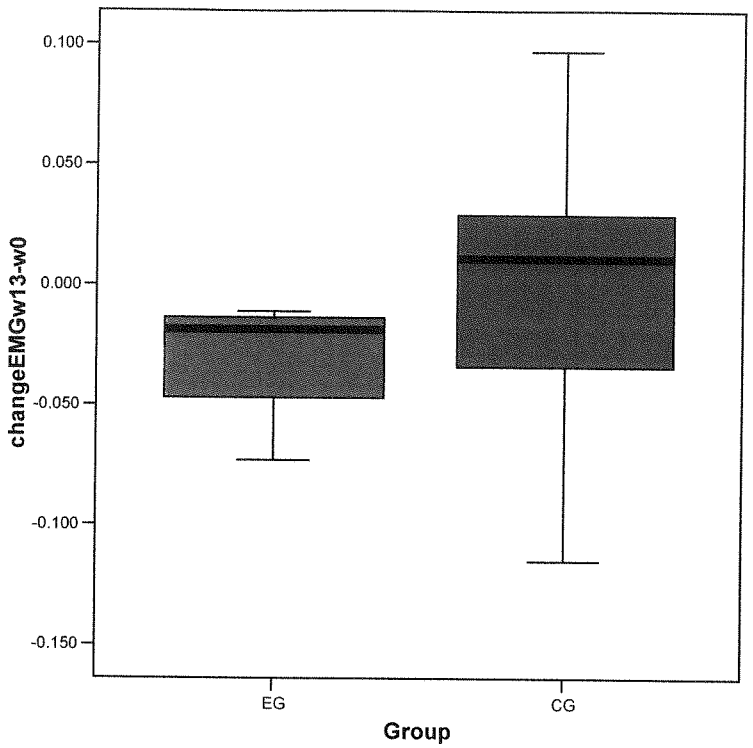


Figure 4.15
Median changes in elbow flexor activity (EMG, mV) from week 0 to week 13
EG: Experimental Group, CG: Control Group

RTPM: from week 0 to week 13

In the EG, changes in RTPM were equivocal (mean change 0.08 N/deg, range -0.17 to 0.39 N/deg), with a noteworthy increase in participant P13[5]. The CG showed a decrease in RTPM (mean change -0.13 N/deg, range -0.40 to 0.12 N/deg), with five out of seven participants showing an improvement.

The difference between the two groups in terms of biomechanically measured RTPM was not significant (U=6.0, p=0.16), fig. 4.16.

[5] Participant P13 had injured his neck and arm one month previously and had only just ceased to take painkillers.

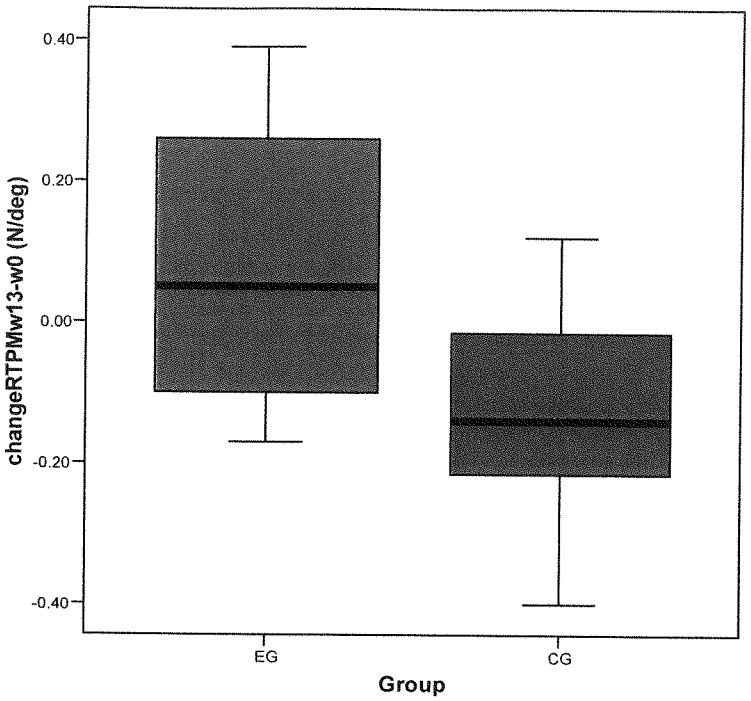


Figure 4.16
Median changes in Resistance to Passive Movement (N/deg): week 0 to week 13
EG: Experimental Group, CG: Control Group

Ashworth Scale: from week 0 to week 13

Compared to baseline, median changes in AS were small in the EG (-0.5, range -1 to 0 point). A decrease of 1 point was noted for participants P06 and P07, whilst no change was seen in P03 and P13. In the CG, the median change in AS was 0 points (range -1 to 0 point), with a decrease of 1 point observed in two and no change in the remaining five participants.

The difference in AS between the two groups over this study period was not significant (U=11.0, p=0.58), fig. 4.17.

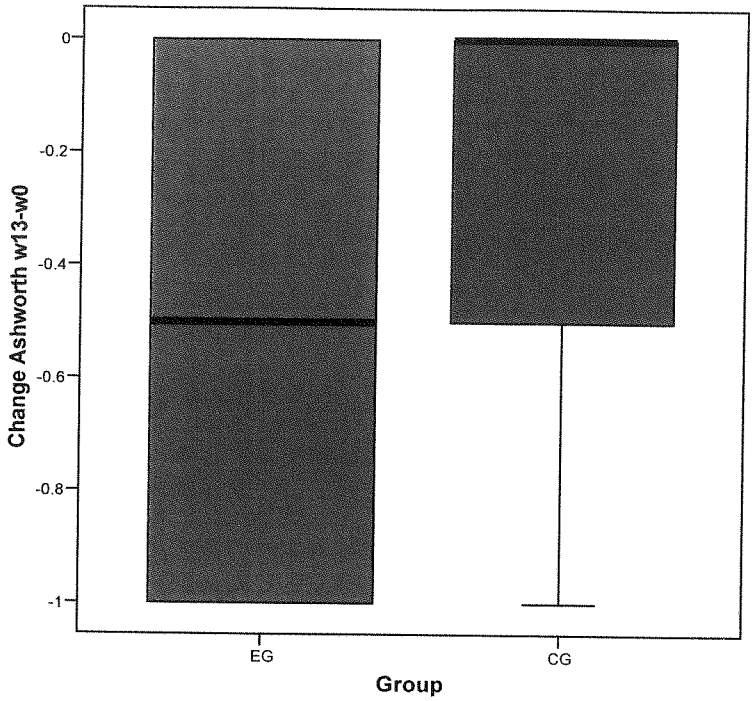


Figure 4.17
Median changes in Ashworth scale for the elbow joint from week 0 to week 13
EG: Experimental Group, CG: Control Group

Grip Force: from week 0 to week 13

In the EG, grip force of the affected hand merely fluctuated (mean change -2.0 N, SD 12.5). In the CG, the mean change was 5.6 N (SD 46.8), with considerable inter-subject variation. Participant P08 demonstrated a remarkable increase (by 101.2 N), whilst participants P09 and P12 deteriorated (by 36.0 and 39.4 N, resp.) and lost most or all of the grip force they had at baseline (Appendix 4.3).

The difference between the two groups in terms of changes in grip force between baseline and end of the study period was not statistically significant (U=14.0, p=1.00), fig. 4.18.

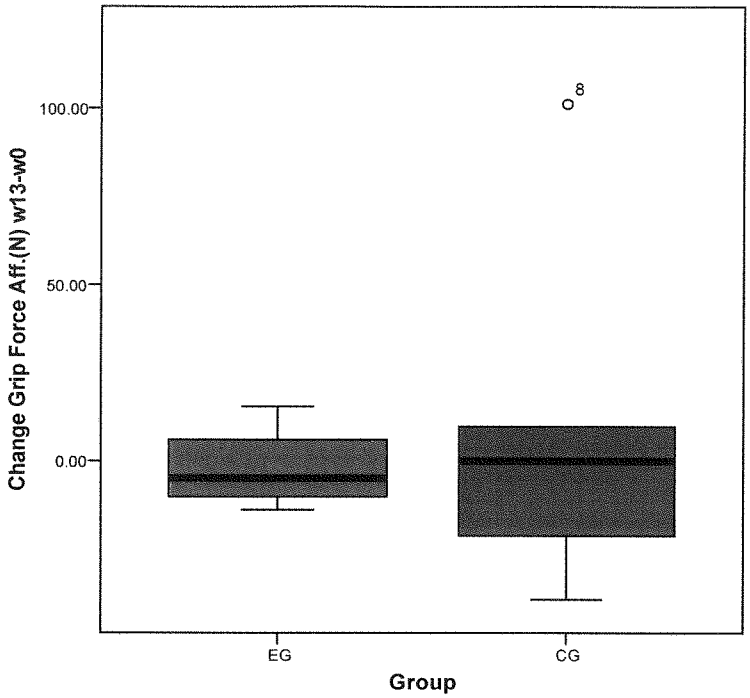


Figure 4.18
Median changes in Grip Force (N) of the affected hand from week 0 to week 13
EG: Experimental Group, CG: Control Group

Stroke Impact Scale: from week 0 to week 13

At week 13, the response rate was four out of five in the EG and five out of seven in the CG.

The EG reported an improvement in ADL (SIS-5) between week 0 and week 13, with positive results in all four participants (median change 11.5%, range 5.0 to 20.0%). In contrast, the CG only showed minimal fluctuations in this variable (median change 0.0%, range -2.5 to 5.0%).

The difference between the two groups in terms of changes in ADL from baseline to the end of the study approached statistically significance (U=0.50, p=0.02) in favour of the EG. Figure 4.19[a] illustrates the improvements in terms of ADL (SIS-5) in the EG compared with the minimal change in the CG.

Hand function (SIS-7) showed a very small median change in the EG (2.5%, range 0.0 to 25.0%), with no or only a minimal change reported by three participants and a considerable improvement in one (P03: 25%). In the CG, hand function showed little overall change (median 0.0%, range -20.0 to 5.0%), although participant P05 reported a 20% decline.

The difference between changes in hand function (SIS-7), was not significant (U= 4.50, p=0.49). Although there was overlap between the two groups in terms of change in hand function (SIS-7, Figure 4.19[b]), the box plot also indicates that all changes in the EG were equal to or greater than zero, in contrast to the CG, which featured mixed results.

In terms of participation (SIS-8), the results were equivocal in the EG (median change 3.2%, range -12.5 to 6.2%). Participant P03 deteriorated by 12.5%, while the remaining four participants showed minimal improvements. In the CG, the median change in SIS-8 was 9.4% (range -21.9 to 40.1%), showing the greatest improvement in P02, followed by P09 (12.5%) whilst P05 noted a decreased score of -21.9%.

The difference in change in participation between the two groups from baseline to end of study was not significant (U=7.0, p=0.56), fig. 4.19[b].

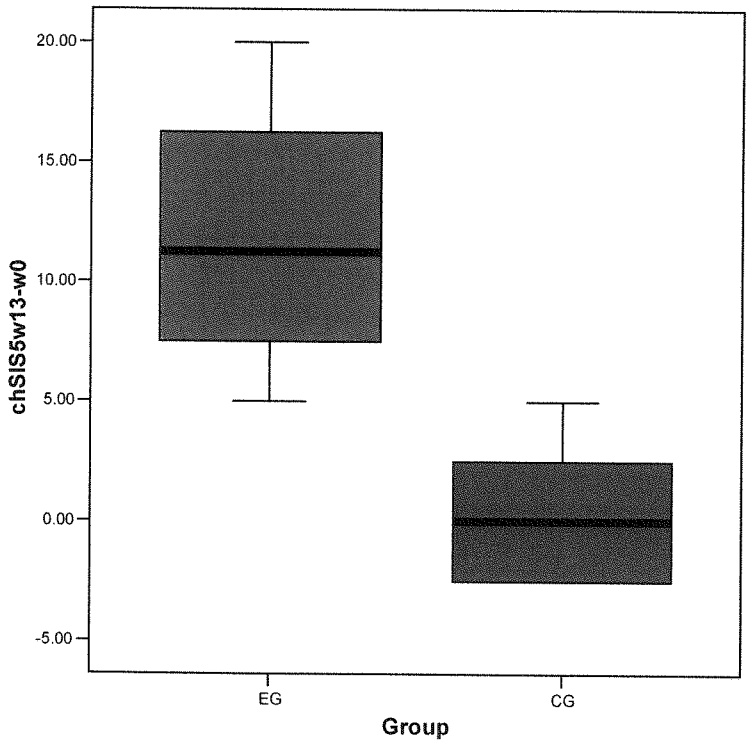
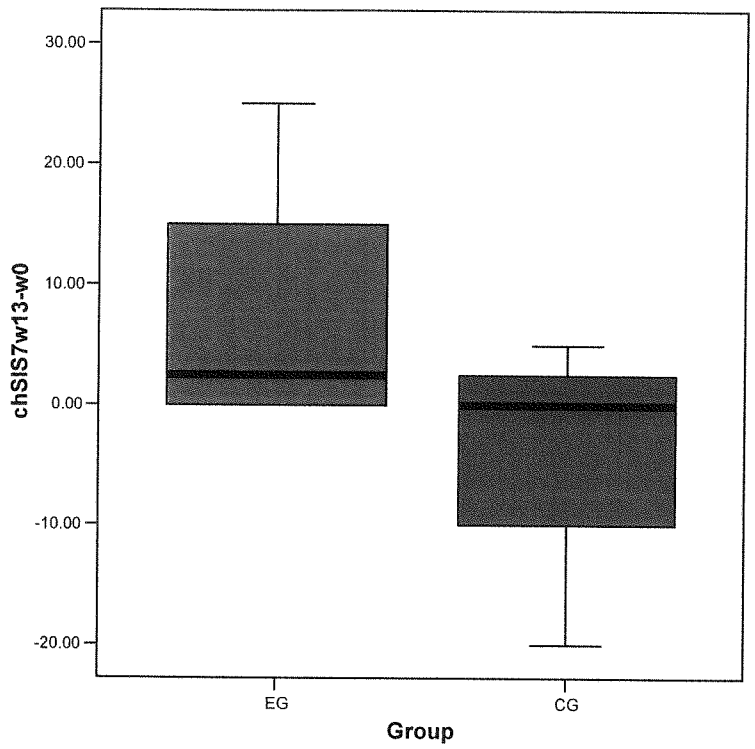


Figure 4.19[a]
Median changes in Stroke Impact Scale (SIS) domain scores (%) from week 0 to week 13
Top: ADL (SIS-5)
EG: Experimental Group, CG: Control Group



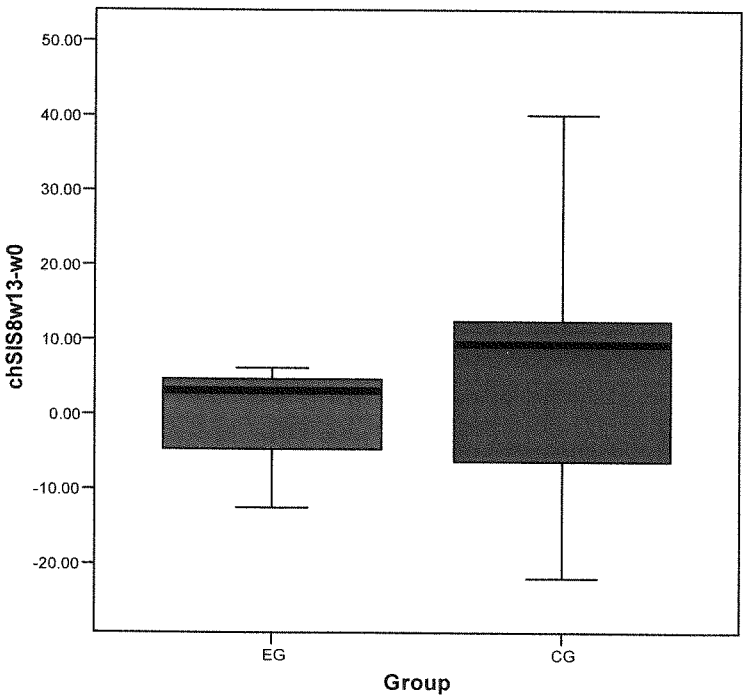


Figure 4.19[b]
Median changes in Stroke Impact Scale (SIS) domain scores (%) from week 0 to week 13
Top: Hand Function (SIS-7); bottom: Participation (SIS-8).
EG: Experimental Group, CG: Control Group

Summary of differential changes between EG and CG (Week 0 to Week 13)

The data pertaining to self-reported ADL (SIS-5) suggested an improvement in the EG of 11% (range 5.0 to 20.0%) compared with 0% (range -2.5 to 5.0%) in the CG (p=0.02), but this differential change did not reach the critical p-value. There were no statistically significant differences between the EG and the CG in terms of any of the other outcome measures.

4.7 BOTULINUM TOXIN TYPE-A TREATMENT AT END OF STUDY

This section describes the BTX-A treatment that was provided following the intervention programme and explores whether there were any significant differences in change of mean dosage, compared to BTX-A treatment at the beginning of the intervention.

Table 4.10[a] provides information about the BTX-A treatment for each of the two groups, while table 4.10[b] lists the details of the injection sites and dosages for each individual participant, following the end of the study at Week 13.

On one occasion in the EG was treatment deferred for a total of seven months (Participant P06). The average dosage in the EG changed from 318 MU (SD=192, table 4.4[a]) at baseline to 264 MU (SD=282) at Week 13.

In the CG, treatment was deferred for three months on one occasion (Participant P14), reducing the average dosage in this group from 402 MU (SD=97, table 4.4[a]) at baseline to 374 MU (SD=169) at Week 13.

At week 13, there was no significant difference between the two groups in terms of BTX-A treatment (U=16.5, p=0.92) and neither was there a significant difference between the two groups in terms of their reduction in total BTX-A dosage (U=12.0, p=0.37) from Week 0 to Week 13.

Table 4.10[a]
Botulinum toxin –type A treatment after the study

EG: Experimental Group. CG: Control Group. Type of toxin: "D": Dysport®[6], "A": Allergan®[7]. MU: mouse units. Injection sites: the frequency indicates the number of participants receiving an injection into a specific muscle (group). Dosage: * Based on Odergren (1998), the dosage for the Allergan product (Botox®) was converted to dosage for the Ipsen product (Dysport®) using the following conversion: Dysport®: Botox® = 3.1: 1.

Botulinum Toxin treatment	EG (n=5)	CG (n=7)	Level of significance
Type of toxin (frequency) Dysport® Botox® Treatment deferred (duration)	 n=4 n=0 n=1 (7 months)	 n=5 n=1 n=1 (3 months)	NA
Mean Total Dosage Dysport®(MU)* SD Min Max	**264** 282 0 650	**374** 169 0 500	ns
Mean change in Total Dosage from baseline Dysport®(MU)* SD Min Max	**15** 255 -400 275	**-29** 180 -400 200	ns

Ns: non-significant

[6] Dysport ®, Ipsen Ltd., Slough, UK
[7] Botox®, Allergan Ltd, High Wycombe, UK

Table 4.10[b]

Botulinum toxin treatment: re-injection following the study

EG: Experimental Group. CG: Control Group. Type of toxin: "D": Dysport®, "A": Allergan®. Injection sites: PM: m. pectoralis major, BB: m. biceps brachii, TB: m. triceps brachii, BR: m. brachioradialis, PT: m. pronator teres, FDS: m. flexor digitorum superficialis, FDP: m. flexor digitorum profundus, AP: m. adductor pollicis, IHM: intrinsic hand muscles. N: number of participants injected in a particular muscle (group). Dosage: * The Allergan dosage was converted to Dysport units using the following conversion: Dysport®: Botox® = 3.1: 1 (Odergren, 1998).

EG Participant ID	**BTX Type**	**PM**	**BB**	**TB**	**BR**	**PT**	**FDS& FDP**	**AP**	**IHM**	***Total***	***Total Converted***
3	D	0	200	0	100	0	3x100	0	0	*600*	*600*
6	NA[8]	0	0	0	0	0	0	0	0	*0*	*0*
7	D	0	300	0	0	0	2x175	0	0	*650*	*650*
11	D	0	0	0	0	0	3x83	0	0	*250*	*250*
13	D	0	150	0	0	50	2x75	0	0	*350*	*350*
Mean (SD)		**0 (0)**	**130 (130)**	**0 (0)**	**20 (45)**	**10 (22)**	**210 (139)**	**0 (0)**	**0 (0)**	**264 (282)**	**264 (282)**
Min		**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Max		**0**	**300**	**0**	**100**	**50**	**350**	**0**	**0**	**650**	**650**
N		**0**	**3**	**0**	**1**	**1**	**4**	**0**	**0**		
CG Participant ID	**BTX Type**	**PM**	**BB**	**TB**	**BR**	**PT**	**FDS & FDP**	**AP**	**IHM**	***Total***	***Total Converted***
2	D	0	250	0	150	0	0	0	0	*400*	*400*
4	A	40	40	0	10	0	2x20	20	0	*150*	*465*
5	D	0	100	0	0	0	2x125	50	0	*400*	*400*
8	D	0	150	0	150	0	2x75	0	0	*450*	*450*
9	D	0	200	0	100	0	2x100	0	0	*500*	*500*
12	D	0	0	0	0	0	4x100	0	0	*400*	*400*
14	NA[9]	0	0	0	0	0	0	0	0	*0*	*0*
Mean (SD)		**6 (15)**	**106 (99)**	**0 (0)**	**59 (72)**	**0 (0)**	**149 (148)**	**10 (19)**	**0 (0)**		***374 (169)***
Min		**0**	**0**	**0**	**0**	**0.00**	**0**	**0**	**0**		***0***
Max		**40**	**250**	**0**	**150**	**0.00**	**400**	**50**	**0**		***500***
N		**1**	**5**	**0**	**4**	**0**	**5**	**2**	**0**		

[8] BTX-A treatment was deferred for 7 months.
[9] BTX-A treatment was deferred for 3 months.

4.8 PARTICIPANTS' PERSPECTIVES

A selection of views, articulated by the study participants, is included in Appendix 4.10. These were distilled from field notes taken during the treatment period by the research physiotherapist - but these were only made available to the assessor after blinding had been removed. Additionally, notes made by the assessor during assessment sessions were included.

4.9 SUMMARY

As explained at the start of this chapter, the results presented in the previous sections must be interpreted with due caution, given the severe limitations of the dataset. Hence, the conclusions offered below are intended to be tentative only.

The aim of this feasibility RCT was to explore whether the changes in outcomes in the EG, where BTX-A had been combined with a functional skill acquisition programme, would be any different from those in the CG, where BTX-A had been combined with a passive intervention (i.e. an inflatable UL splint).

At baseline, there were no significant differences between the two groups in any of the dependent variables. Overall, changes in any of the outcomes in the CG were negligible - apart from the COPM-S, which improved in both groups.

Between baseline and immediately following the therapy programme at Week 4, the EG improved in self-rated performance of self-selected goals (COPM-P) with a median change of 3 points (range 1.5 to 5.0 points), compared with 0.5 points (range -2.0 to 3.5 points) in the CG ($p=0.06$). This coincided with an improvement in self-reported hand function (SIS-7) in the EG (median improvement 25%, range 0.0 to 30.0%), whilst the CG noted a median change of 0.0% (range -10.0 to 0.0%, $p=0.04$). Neither of these differential changes reached the critical p-value.
Between baseline and mid-point of the study at Week 7, the EG showed a significant improvement on the standardised arm function test (ARAT), with a

median change of 4 points (range 1 to 8 points), compared with a median decrease of 1 point in the CG (range -3 to 0 points; p=0.003).
From baseline to the end of the study period at Week 13, self-reported ADL (SIS-5) improved in the EG by 11% (range 5.0 to 20.0%), compared with 0% (range -2.5 to 5.0%) in the CG (p=0.02). Although this difference did not reach statistical significance, it was nevertheless noteworthy, since it occurred nine weeks after the completion of the therapy programme.
There were no other statistically significant differences between the EG and the CG in any of the other outcome measures

Given the exploratory nature of this pilot study, calculation of the effect size was omitted. However, given the reported minimal clinically important differences (MCIDs) for the ARAT (i.e. 6 points, van der Lee et al., 1999), the SIS (i.e. between 10-15% Duncan et al., 1999) and the COPM (i.e. 2 points, Mirkopoulos and Butler, cited in Law et al., 1998), it is nevertheless clear that clinically relevant improvements occurred more frequently in the EG than in the CG.

Regarding spasticity and resistance to passive movement, it is worth noting that there was hardly any change in elbow flexor activity (EMG) in either group throughout the entire study. There were no statistically significant differences between the two groups in terms of change in EMG at any point in time.
Biomechanically measured RTPM increased in the EG over the first seven weeks, in contrast to the CG, where it tended to decrease. However, there was no statistically significant difference in change in RTPM between the two groups over any of the study periods.
The Ashworth Scale tended to improve by 1 point in both groups between baseline and Week 4 and returned to baseline, usually between Week 7 and 13, but again there were no differential effects between the EG and the CG over any of the trial phases.

Common adverse events were fatigue and transient upper limb pain. No serious treatment-related adverse events occurred although three serious, non-treatment related incidents were reported. The treatment schedule *per se* was felt by many as intensive, although only one of the participants felt this to be a problem. Those

randomised into the EG generally found the intervention to be enjoyable, while any changes reflected improvements in UL function. Quite surprisingly, although one person in the CG commented that the programme was somewhat tedious, there were no negative comments on this type of intervention. Most of the changes that were reported in this group reflected reductions in perceived stiffness, tightness, or range of movement.

Chapter Five will proceed to discuss these results and highlight the main limitations and sources of error of the study. The findings will be placed in context by comparing and contrasting them with similar work in the literature. Finally, recommendations for future clinical practice and research will be formulated.

CHAPTER FIVE

SKILL ACQUISITION AND BOTULINUM TOXIN FOR CHRONIC UPPER LIMB SPASTICITY AFTER STROKE: A FEASIBILITY RCT - *DISCUSSION and CONCLUSIONS*

5.1 INTRODUCTION

The primary aim of the feasibility RCT, reported in Chapters Three and Four, was to investigate whether a functional, evidence and theory-based skill acquisition programme, administered after botulinum toxin type-A (BTX-A), would have any differential effects on upper limb (UL) spasticity or functional activity in people with chronic UL spasticity following a stroke.

Functional activity involving the affected UL was assessed in terms of performance on a standard test (i.e. the Action Research Arm Test, or ARAT), a patient-centred outcome measure (the Canadian Occupational Performance Measure, or COPM). Spasticity was measured as elbow flexor activity (EMG) during brisk, passive elbow extension, while resistance to passive movement was rated using a standard clinical scale (the Ashworth Scale, or AS), which was instrumented to yield additional biomechanical data (resistance to passive movement, or RTPM). Grip force was measured with a standard Jamar dynamometer. Furthermore, participants' perceptions of any changes in hand function, ADL and participation restrictions were explored using a validated, published self-report measure (i.e. the Stroke Impact Scale, or SIS). The primary outcome measures were: ARAT, COPM and EMG.

In the following sections, the results will be interpreted in the context of relevant literature, i.e. BTX-A, exercise therapy in general and task-specific training in

particular, with or without mental practice (MP). Study limitations and sources of error will be highlighted and their potential impact on the results will be discussed. Finally, the implications of this feasibility study for clinical practice and research will be explored.

5.2 INTERPRETATION OF THE RESULTS

5.2.1 CONTEXT: SAMPLE CHARACTERISTICS

In order to be able to interpret the results, it is important to place them into context. As section 4.2 and table 4.2 indicated, participants had generally good cognitive and communicative abilities. These characteristics were congruent with the eligibility criteria of the study (box 3.2). However, adhering to these strict criteria also meant that the resulting study sample was very small and select. In addition, the intensity of the programme required a high level of motivation and general health. It is likely that those suffering from common stroke-related problems such as fatigue and/ or depression (Staub and Carota, 2005) or those with other health issues would have been discouraged by the prospect of such an intensive programme. Additionally, those who were employed on a full-time basis could not take part. Transport facilities may also have influenced the study sample, since given the lack of funding, participants were required to make their own travel arrangements. Those unable to do so, may have declined the invitation.

Regrettably, due to a lack of resources, it was not possible to formally screen and register all patients attending the Spasticity Outpatient Clinic. Thus, many more patients may have declined the invitation to take part in the study or may not have been considered to be eligible before they could be contacted by the study coordinator. In future research, it is recommended that all patients be logged (cf. the CONSORT Statements [http://www.consort-statement.org/] in order to obtain a comprehensive picture of this patient population, their symptoms and their needs.

Altogether, the results from this study pertain to a very select subpopulation of people with a stroke and therefore have limited external validity. Further research with a more representative sample is required before the findings may be generalised.

In the study group as a whole, participants rated their overall recovery between 20% and 70% on the SIS (table 4.2[b]). Domains showing considerable limitations were: upper limb function (notably hand function: median SIS-7 score for both groups was 0%), strength in the affected extremities (SIS-1) as well as participation (SIS-9). Interestingly, activities of daily living (ADL, SIS-5) were only moderately affected. Noteworthy were the very low scores on all indices of upper limb function: both groups scored a median of 10 points out of 57 on the ARAT (i.e. approximately 17.5% of normal performance), 3 points out of 10 on the COPM-P (i.e. approximately 33%), while average hand ratio (i.e. the ratio of maximum voluntary grip force of the affected hand to that of the non-affected hand) was only 16%. In summary, these data clearly show that, in terms of upper limb function, both groups in the study sample had very severe limitations.
The SIS data at baseline also showed that the stroke was perceived to have had considerably less impact on participants' cognition, emotion, communication and mobility functions.

In terms of the ability to use movement imagery, there was a wide range of scores in both groups, especially in the EG (Appendix 4.1). Compared with the normative data for young adults from Eton et al. (1998)[1] suggests that in this study, the participants in the CG scored better than the non-impaired controls, both in terms of the $VMIQ_{self}$ and the $VMIQ_{other}$. Those in the EG produced similar results as non-impaired controls in the $VMIQ_{other}$.domain, but scored considerably poorer in the $VMIQ_{self}$ domain. Interestingly, in the non-impaired sample in the study by Eton et al. (1998), there was approximately a 10% difference between $VMIQ_{self}$ and the $VMIQ_{other}$, with visualising oneself being more difficult than visualising a third person. This relationship also held for the participants in this study, but the difference was much greater (i.e. approximately 80% in both groups). This suggests that the stroke may not have affected visualisation with regards to others, but may have impaired the way in which one is able to visualise oneself. This may have important implications for the efficacy of mental practice, but the cohort was too small in this study to analyse the effect of the VMIQ scores as a covariate, as had been planned

[1] In the study by Eton et al. (1998), non-athletes scored as follows: VMIQ self: mean = 61 (SD 17), VMIQ other: mean = 55, (SD 17).

originally. However, the impact of visual movement imagery ability on the use of MP requires further research in future.

5.2.2 NOTES OF CAUTION

Prior to interpreting the data, it is also necessary to consider further limitations of the dataset, in addition to the very small and selective sample, namely the non- normal distribution, the ordinal level nature of some of the primary outcome measures and missing data. These features imposed severe restrictions on the methods of analysis as well as the interpretation of the data. Additionally, the relatively large number of statistical tests, performed on multiple outcome measures at three points of assessment, augmented the experimentwise error rate (Field, 2000). Given these methodological issues, any conclusions pertaining to statistical significance in this section should therefore be viewed with due caution and considered as tentative only.

In the following sections, the differential effects of the interventions will be summarised and compared and contrasted in terms of upper limb activity, grip force and finally measures of resistance to passive movement and spasticity.

5.2.3 DIFFERENTIAL EFFECTS ON UPPER LIMB ACTIVITY

Standard measures (ARAT)

Comparing baseline with Week 7 (i.e. 3 weeks after the end of the intervention programme), the EG showed significantly greater benefit than the CG ($p=0.003$) with an improvement in all participants in the EG, whereas changes in the CG were absent or negative. However, comparisons over any of the other study phases did not yield any significant differences. Over the 13-week study period, ARAT changes in the CG showed small fluctuations only (i.e. between -3 and 2 points), some of which could possibly due to measurement errors. In contrast, changes in the EG varied between -4 and 9 points, which would be more likely to indicate an actual difference in performance. Following individual participants in the EG, it emerged that participants P03 and P07 showed virtually no change, whereas P06, P11 and P13 did improve.

In terms of clinical significance, van der Lee *et al.* (2001b) suggested that the minimal clinically important difference (MCID) for the ARAT be 10% of its range, i.e. 6 points. Applying this to the current study, it is clear that the CG consistently failed to reach this criterion. Although most changes in the EG were below the MCID, three of the five participants (P06, P11 and P13) demonstrated changes of such magnitude. While acknowledging that the ARAT changes were generally quite small and that at the end of the study, the median ARAT score in the EG was 9.5 points only (range 4 to 20, Appendix 4.8), it is worth placing them against the background of the baseline scores (table 4.2[a]): most participants were severely impaired on the ARAT and it is debatable whether a difference of 6 points would have been a realistic goal.

The question as to why some participants in the EG improved and others did not, can unfortunately not be answered through this study, given the properties of the dataset, which prevented stratification as well as the determination of covariates. A number of authors suggested that sub-acute stroke patients with only mild impairments may derive more benefit from additional UL rehabilitation than those with more severe impairments (e.g. Sunderland *et al.,* 1992; Parry *et al.,* 1999). In contrast, Feys *et al.* (1998, 2004) noted that additional sensorimotor stimulation of the affected arm was more effective in patients with a severe motor deficit, hemi-anopia and hemi-inattention. It is likely that treatment success depends on the interaction between the specific nature of the deficits and the effects of the intervention.

In this study, two pairs of participants started off at the same ARAT baseline score, but their progress was markedly different. Participants P03 and P06 both started at an ARAT score of 4 points, but whilst P03 showed hardly any change, P06 reached the MCID between baseline at Week 7. The details on BTX-A treatment (table 4.4 [a,b]) showed that the dosage for the forearm flexors was identical in these cases, but that P03 was given a higher dosage into the proximal UL musculature than P06. From Appendix 4.10, it can be gleaned that the therapist experienced difficulties with mobilising the hand and that problems were encountered with most activities in the programme. In addition, any improvements seemed to occur in the proximal rather than the distal UL joints. These findings suggest that the amount of distal control could be a factor in the extent to which upper limb function may be regained following BTX-A, a suggestion also put forward by Rousseaux *et al.* (2002).

Participants P07 and P13 also started off at the same ARAT level, but while the former did not improve, the latter achieved the MCID, despite a severe injury during the last phase of the study. The pattern of spasticity in P07 was unusual: the m. triceps brachii was injected and a relatively large dosage was administered to the m. flexor digitorum superficialis. Upon reassessment, this gentleman reported loss of strength in his thumb, while hypertonicity of the m. triceps brachii appeared to cause problems with elbow flexion. Case notes on P07, consulted after blinding of the assessor had been removed once data analysis had been completed, suggested that the nature of the particular motor control problem in this case remained unclear and that the optimal pharmacological intervention had not yet been established. Although it would have been better if the BTX-A intervention had been optimised before entering the study, omitting the data from this participant was not considered to be a justifiable option on the basis of the existing eligibility criteria, although it was acknowledged the data may have confounded the results. In future studies, it could be requested that BTX-A treatment be optimised prior to entering a study of a similar design.

Regarding the timing of the ARAT changes, it was perhaps surprising to find a significant improvement in the EG compared to the CG between baseline and Week 7, since the therapy programme had finished three weeks earlier. This may be explained by learned non-use, which in some cases may have been prevalent for years. For example, participants P06 and P11 in the EG (who were five ten years after stroke, respectively) mentioned that they had been challenged to think about new ways of using their affected arm and this suggests that new neuromuscular pathways were developed during the programme. However, with long-standing procedural memories involving the (non-) use of their affected side, it is plausible that pro-active interference, (i.e. when former memories hamper the development of new ones) may have been responsible for some delay. It would be reasonable to assume that, in the chronic stage after stroke, frequent practice would be required over a considerable period of time for long-term neuroplastic changes, (e.g. long-term potentiation) to occur. Additionally, from a biomechanical perspective, improvements in ROM and force also require time. Taken together, these factors may explain why, particularly in the case of participant P06, it may have taken some time for changes in UL function to occur.

A direct comparison between the findings from this study and the literature was not possible, since as at the time of writing there was no similar investigation in the published domain. A comparison with related work on UL BTX-A in stroke rehabilitation (section 1.3) is limited to two investigations, as only the studies by Simpson *et al.* (1996) and Bakheit *et al.* (2000) employed a validated UL outcome measure. These studies did not find any improvements in UL function. However, whether any therapy input was provided that may have targeted function was not reported.

Although a comparison with non-RCTs will not be undertaken because of the difficulties with the interpretation of the findings, contrasting the findings with the pilot study, reported in Chapter Two, may nevertheless be valuable. Since the treatment in that study consisted of BTX-A only, it enables the impact of the placebo intervention in the current study to be explored. In the pilot study in Chapter Two, ARAT scores improved significantly from baseline to Week 4 (table 2.7), although the median change was 0 points (range -1 to 6 points) and only one participant out of 14 reached the MCID. In the current study, the median ARAT change in the CG was 0 points (range -2 to 1 point), whilst in the EG this was 2 points (range -2 to 9 points), with three out of five participants achieving the MCID or over. The apparently greater effect in the first pilot study than in the CG in the current study could be explained by a number of factors: firstly, a lack of blinding could have elicited experimenter bias in the first pilot study. Secondly, as the subjects in the first pilot study were not given any formal therapy, some may have engaged in independent practice at home, which may have confounded the results. Alternatively, the possibility that BTX-A improved arm function in some individuals without any concurrent therapy needs to be considered. However, the finding that only one out of 14 participants reached the MCID in the first study, compared to three out of five in the current RCT, suggests that the likelihood for this to occur is lower than when additional therapy is provided.

Comparing this study with the literature on UL exercise therapy in general within stroke rehabilitation (i.e. without BTX-A) is restricted, as the literature is dominated by studies involving (sub) acute patients (e.g. Winstein *et al.,* 2004; Woldag *et al.,* 2003; Dromerick *et al.,* 2003; Rodgers *et al.,* 2003; Page *et al.,* 2001c);

Langhammer and Stanghelle, 2000; Volpe *et al.,* 2000; Kwakkel *et al.,* 1999; Duncan *et al.,* 1998; Feys *et al.,* 1998; Lincoln *et al.,* 1999; Mudie and Matyas, 1996; Gelber *et al.,* 1995; Sunderland *et al.,* 1992, 1994; Jongbloed *et al.,* 1989; Logigian *et al.,* 1983). The relatively few RCTs conducted in the chronic stage after stroke rarely involved people with upper limb impairments as severe as in the current study. For example, investigations into Constraint Induced Therapy (e.g. van der Lee *et al.,* 1999; Taub *et al.,* 1993, 1998) all limited inclusion to those with at least some active wrist and finger extension. The baseline ARAT score in the sample in the study by van der Lee *et al.* (1999) was approximately 30 points, compared to 10 points in the current study. Since ARAT performance at baseline has been shown to be a significant covariate (van der Lee *et al.,* 1999), a valid comparison of the efficacy of different upper limb treatments can only be made if this variable is taken into the equation.

Comparing this study with other work featuring task-specific practice is hampered by differences in treatment content and intensity. For example, CIT features functional tasks, but per definition excludes any bimanual activities. The traditional CIT training schedule[2] (Taub *et al.*, 1993) is far more intensive than that employed in the current RCT. The task-related training protocol, described by Thielman *et al.* (2004) exclusively featured unilateral reach and grasp tasks, whereas the current study used a wider range of activities. In the study by Thielman *et al.* (2004), between 150 and 180 movements were carried out per session, which again was far more than in the current study with 45 activities per session, using different practice techniques. The number of activities in the current study was based on pilot work with people with similar arm function characteristics and represented a maximum realistic number of activities in a 45-minute period.

A comparison between the current study and other RCTs using mental practice (MP) after stroke is not appropriate, mainly because the research question in published studies pertained to the efficacy of MP – whereas in the current study, the

[2] Taub *et al.* (1993) applied restraint of the non-affected arm for 90% of the waking hours, while practice was undertaken 6 hours, 5 x per week for 2 weeks (i.e. a total of 60 hours of practice alone). The total amount of practice undertaken in the current study was 15 hours.

efficacy of a comprehensive skill acquisition package – of which MP was one component – was evaluated.

Patient-centred measure (COPM)

The diversity of issues emerging from the COPM at the start of the study (table 4.3) was fascinating. Most of these related to self-care and productivity, while a considerable proportion was associated with leisure. It was also of interest to note that some participants articulated very few UL-related problems (e.g. P04), which suggested that the affected UL as an "issue" may not necessarily have been of great importance to some participants. It would be reasonable to assume that the number of UL-related issues may have affected participants' motivation to participant in the programme, but this was not formally assessed. However, the high attendance figures (table 4.6) gave an indication that participants came for treatment whenever they could. The finding that the affected UL was not "an issue" for some participants raises an important question on the ethics of the intervention programme, which will be addressed in section 5.5.

As indicated in table 4.2[a], both the COPM-P and COPM-S scores were very low at baseline. Although there were no significant differences in COPM changes between the two groups over the course of the study, it was interesting to find a greater improvement in the EG than in the CG between baseline and Week 4 ($p= 0.06$). The change in the EG (median= 3.0 points, range 1.5 to 5.0 points) could be compared to an improvement of approximately 33%, compared to less than 6% in the CG (median = 0.5 points, range -2.0 to 3.5 points). Mirkopolous and Butler (1994, cited in Law *et al.*, 1998) suggested that a change of 2 points on the COPM constituted a clinically relevant change. Thus, more clinically relevant improvements in self-selected occupational activities tended to occur in the EG than the CG in the first study phase.

Interestingly, changes in satisfaction with performance (i.e. the COPM-S) were comparable between the two groups. Between baseline and Week 4, there was a considerable increase in both groups (equivalent to 28% in the EG and 22% in the CG). The rise in the CG, in the absence of corresponding changes in performance, was rather surprising. One explanation could be that attention from the research

physiotherapist acted as a placebo. Alternatively, over the course of the study, some participants may have reassessed the importance of some of the issues raised initially and adjusted their scores accordingly. This would be congruent with findings reported by Cup *et al.* (2003), who showed that treatment goals tended to change over time, with just over half of the number of goals identified originally being listed again only eight days later. This suggests that goals that are felt to be important at one point in time may change in salience and this may be reflected in the COPM-S scores.

A direct comparison between the results from this work and other research on BTX-A is not possible, since none of the studies, reviewed in section 1.3, or indeed any of the upper limb rehabilitation studies described in section 1.5, featured the COPM. However, a number of BTX-A investigations did attempt to include the patient's view in their assessment. Subjective global assessment was included in four of the seven RCTs (Bakheit *et al.,* 2001; Brashear *et al.,* 2002; Childers *et al.,* 2004; Simpson *et al.,* 1996), but since there was no evidence that these tools had been validated, the robustness of those findings is questionable. In any case, they did not provide any information on the actual nature of the treatment effects. One exception was the study by Brashear *et al.* (2002), which featured the Disability Assessment Scale. Of its four sub-domains (i.e. hygiene, dressing, limb position and pain), they invited the patient or carer to select one as their principal target, against which progress was then scored. On these targets, significantly greater improvement was found in the experimental group than in the control group, which received placebo injections.

Regarding satisfaction following the intervention, the findings from the placebo groups in the studies by Bakheit *et al.* (2001) and Brashear *et al.* (2002) may be useful to explain the improvements in COPM-S scores in the current study. Bakheit *et al.* (2001) reported that 50% of those in the placebo group indicated they had obtained some or much improvement, while in Brashear *et al.* (2002), this figure ranged from 29 to 48%. Although the nature of the placebo control condition varied between studies (i.e. a passive treatment in the current study and a sham injection in the others), mere contact with a health professional and possibly a belief in the efficacy intervention may have been instrumental in raising satisfaction levels.

Altogether, the lack of patient-centred outcome measures in the upper limb rehabilitation literature in general and BTX-A literature in particular was noteworthy. This implies that it is still largely unknown whether any of the treatment effects are actually considered to be relevant by the service users. It is evident that future research on upper limb treatment after stroke needs to include a patient-centred assessment tool to address this crucial issue.

Self-reported activities (SIS)

Changes in the SIS domains for ADL (SIS-5) and hand function (SIS-7) indicated differences between the two groups during various stages of the study in favour of the EG, while there was no differential effect in terms of participation (SIS-8).

At baseline, all participants considered their hand function (SIS-7) to be very poor (pooled data from both groups: median =0%, range 0 to 30%). Improvements in hand function in the EG improved more than in the CG ($p=0.04$) between baseline and Week 4, with the median improvement in the EG being 25% (range 0 to 30%), compared with 0% (range -10 to 0%) in the CG. Duncan *et al.* (1999) suggested that a change between 10 and 15% on the SIS constituted a clinically relevant difference. Hence, although these differential changes did not reach statistical significance, it appeared that in the EG the intervention produced greater clinically relevant improvements than in the CG. Interestingly, the changes in the EG seemed to be more congruent with the COPM-P than with the ARAT results. When comparing the content of the three scales, this is not surprising; only one of the items on the SIS-7 (i.e. "pick up a dime") resembles an ARAT item (i.e. "pick up a washer"), whereas the SIS-7 items had more in common with the issues noted on the COPM.

The data on the ADL domain of the SIS (i.e. SIS-5) suggested an improvement in favour of the EG between baseline and the end of the study ($p=0.02$), although this differential change did not quite reach the critical p-value. The median change in the EG was 11% (range 5.0 to 20.0%), compared to 0.0% (range -2.5 to 5.0%) in the CG. The suggestion that carry-over had occurred in the EG was perhaps not surprising, as the SIS-5 features a range of ADL categories (e.g. feeding, dressing,

and household tasks), most of which had featured in some form or other in the skill acquisition programme – although the SIS items had not been targeted for the intervention as such. Given the specificity of learning principle (Magill, 2001; Proteau *et al.,* 1992), carry-over would be expected in cases where there was congruency between the training and transfer tasks. However, what was surprising was the timing of this result, i.e. nine weeks after the treatment programme had finished and at a time when BTX-A would no longer be expected to have had an impact. Considering the duration of the UL impairments and activity limitations of most participants, it is plausible that a considerable amount of time was necessary to counteract learned non-use and relearn ADLs to a level where actual change became apparent.

In terms of participation (SIS-8), there were no significant differences between the two groups over any of the study periods. Furthermore, within each group, any median change in SIS-8 was less than 10%, which suggested that neither intervention programme had a clinically relevant impact on participation. This could be explained by the fact that participants in this study may have learned to participate in social roles, religious activities and leisure without active involvement of their affected arm, given the chronicity of their UL impairments. Additionally, most participants were unemployed.

Direct comparisons between this study and other investigations on BTX-A could not be made, as none had included the SIS. Instead, most had used general health questionnaires (e.g. the SF-36) or ADL scales (e.g. the Barthel Index). As discussed in section 1.3, the findings from those studies highlighted the lack of impact of BTX-A on global function (Simpson *et al.*, 1996), independence (Bakheit *et al.,* 2000, 2001; Childers *et al.,* 2004; Simpson *et al.,* 1996) and disability (Bhakta *et al.*, 2000), for which the limited sensitivity and specificity of the scales were thought to be mainly responsible (Bakheit *et al.*, 2000, 2001). In contrast, in studies where specific ADLs had been included as outcome measures, the results were often quite different (see Hesse *et al.,* 1998; Bhakta *et al.,* 2000; Bakheit *et al.,* 2000, 2001 and Brashear *et al.* 2002). Hesse *et al.* (1992, 1998), followed by Bakheit *et al.* (2000, 2001) and Bhakta (2002), selected items such as putting the affected arm through a sleeve, opening the hand for cleaning its palm and cutting finger nails as outcomes,

which did show responsiveness to treatment. Although the strength of these test items is that they were relevant for their study population, it is unclear whether they refer to active function on behalf of the patient or the carer. Additionally, as explained in section 1.3, there was no evidence that these items had been validated.

Simpson *et al.* (1996) explained the absence of ADL improvements in the chronic stage after stroke by suggesting that most people would have found adequate solutions for many of their ADL challenges without necessarily involving their affected arm. This idea has been articulated by other authors (e.g. Platz *et al.*, 2005; Page *et al.* 2005) and is further supported by the data from the current study: the juxtaposition of SIS scores on hand function (SIS-7) and ADL (SIS-5) at baseline (table 4.2[b]) constitutes clear evidence that people may be quite proficient in their ADLs with a minimum of function of their affected hand.

Comparing this study with findings from RCTs on UL exercise therapy with people in the chronic stage after stroke is restricted also, as none of them featured the SIS. In fact, only a few studies used any validated self-report measures on upper limb function or activity (see van der Lee *et al.,* 2001; Hiraoka, 2001), which reveals a remarkable limitation of the evidence base. The only comparable studies were Taub *et al.* (1993) and van der Lee *et al.* (1999). Exploring the effects of CIT in a RCT with nine chronic stroke patients, Taub *et al.* (1993) found marked improvements in daily arm use as well as quality of movement in the experimental group, using the Motor Activity Log (MAL). This effect was maintained at two-year follow up, compared to a control group that was not given any active training. In a RCT with 66 chronic stroke patients, van der Lee *et al.* (1999) found significantly more improvement on the amount of use (but not the quality of movement) of the MAL during two weeks of CIT than bimanual training, but this difference disappeared during follow-up at three, six and 52 weeks after the start of the training - suggesting a performance effect only. However, as indicated previously, subjects had much better arm function at baseline and training was considerably more intensive than in the current study, which may explain the superior effects following CIT compared to no active training.

Comparing this study with findings from RCTs using MP in upper limb rehabilitation, only Dijkerman *et al.* (2004) and Page *et al.* (2005) used a self report measure. Dijkerman *et al.* (2004) employed the Modified Functional Limitations Profile and although a significant difference was found between the MP and the control group, this represented a deterioration for the latter with no improvement in the former. However, the lack of improvement in the MP group is perhaps not surprising as the content of the programme (i.e. picking up blocks or rounded buttons) appeared to be of limited functional value. In contrast, Page *et al.* (2005) trained functional tasks in a randomised controlled multiple baseline study with 11 chronic stroke patients. Compared to the control group, the MP group demonstrated clinically relevant improvements in both daily activity and quality of movement of the MAL. However, only one post-test was used and therefore longer-term effects could not be ascertained.

5.2.4 DIFFERENTIAL EFFECTS ON GRIP FORCE

Prior to interpreting the results, it is important to highlight the conclusions from the calibration study on the Jamar dynamometer (Appendix 3.5), which showed that the accuracy and precision of the instrument were unsatisfactory for forces below 107.8 N (11 kgf). The grip force data at baseline (table 4.2) showed that only one participant (P08) was capable of producing a force that exceeded this level. Data collected at follow-up additionally indicated that this situation did not change during the study (Appendices 4.4, 4.6 and 4.8).

Taken together, these observations meant that the data on grip force in this study could not be interpreted in a meaningful way. Although the Jamar is the most frequently used and widely reported instrument for measuring grip force (Richards and Palmiter-Thomas, 1996; Innes, 1999), it is clear that for a population such as the one in the current study, this instrument was not appropriate and that an alternative will be required for future research.

5.2.5 DIFFERENTIAL EFFECTS ON MEASURES OF RTPM AND SPASTICITY

The data discussed in this section pertain to the group as a whole, since the number of participants injected with BTX-A into their elbow flexors was too small for a subgroup analysis.

EMG data appeared to merely fluctuate in both groups over the 13-week period, with the largest average change in EMG (EG, Week 0 to Week 7, Appendix 4.7) constituting less than 2% of the average level at baseline. In comparison, the decrease in EMG was more marked in the pilot study on BTX-A, reported in Chapter Two.

In contrast, changes in RTPM over time were more marked. In the EG, average RTPM increased by approximately 13% between baseline and Week 4, whereas in the CG, this figure decreased by 35%.

In contrast to the biomechanical RTPM data, the changes in the two groups in terms of the AS were similar: between baseline and Week 4: a decrease of 1 point was found in most cases, signalling a reduction in resistance to passive movement. The consensus in the literature, reviewed in section 1.3, is that a reduction of 1 point on the AS is considered to be clinically significant (Albright et al., 1993) and therefore the reductions in resistance to passive elbow extension may be interpreted as clinically meaningful. Comparing the AS findings with similar work, the change was congruent with that reported in other RCTs (Simpson *et al.,* 1996; Hesse *et al.,* 1998; Bakheit *et al.,* 2000, 2001; Bhakta, 2000, Brashear *et al.,* 2002; Childers *et al.*, 2004).

The spasticity data, measured with the DATA system, could only be compared with the pilot study in Chapter Two, as none of the RCTs on BTX-A employed this particular technology. However, since there were differences between the EMG systems used in the two studies, it was not possible to compare the absolute values of the EMG data.

With respect to elbow flexor activity, the pilot study in Chapter Two had shown a reduction in EMG four weeks following BTX-A (albeit not statistically significant,

table 2.6), but in the current study, the results were mixed in both groups (Appendix 4.5). This may be explained by the fact that in the BTX-A pilot study, all participants had received injections into their elbow flexors, whereas in the current study, this was only the case in two out of five participants in the EG and six out of seven in the CG. As explained earlier, the subset of participants with BTX-A injected into their elbow flexors was too small for a separate analysis, but this should be undertaken in future work, where sample size allows.

In the BTX-A pilot study, no significant change had been found in RTPM between baseline and four weeks following BTX-A – in fact, mean RTPM had increased by 6% by week 4. In this study, the increase in the EG was greater than in the pilot study, whereas the CG demonstrated a clear decrease in RTPM. Both studies had been drawn from a chronic population where permanent soft-tissue changes were likely to be common. However, in the pilot study, no additional intervention had been given whereas in the current study, two very different interventions had followed on from BTX-A. The difference between the EG and the CG could be explained by the effects of the stretching and splinting protocols in the current study as will be explained next.

Based on the work by Bobath (1969), one of the concerns at the start of the study had been that the activity, associated with the skill acquisition programme in the EG, would elicit an increase in spasticity. It was therefore reassuring to find that there were no significant differences in elbow flexor EMG between the two groups over the course of the study. However, biomechanically measured RTPM showed an increase in the EG up to Week 7, whereas it decreased considerably in the CG. The corresponding EMG data suggested however, that the increase in the EG was not associated with actual spasticity, as interpreted by the SPASM consortium (Pandyan et al., 2005: p.5[3]). Instead, it was more likely to be attributable to biomechanical changes. The splinting protocol, whereby participants in the CG were resting for 30 minutes at a time with their affected upper limb in a stretched, static position, together with the lack of any activity, could have resulted in any crossbridges between actin and myosin being detached, thereby reducing

[3] "*Disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles*" (Pandyan *et al.*, 2005: p. 5).

biomechanical stiffness. In contrast, daily activity involving the affected upper limb in the EG may have increased the number of crossbridges between actin and myosin, thereby increasing the biomechanical contribution to RTPM.
However, even though the mean increase in RTPM was considerable in the EG, especially between baseline and Week 7 (Appendix 4.7), the question needs to be asked whether this was actually clinically relevant. It was therefore interesting to find that increases in AS were not common over the first seven weeks of the study and that the maximum increase in AS was 1 point in only one participant (P11). This suggests that the magnitude of most of the changes in RTPM in this study may have been at a sub-clinical level.

Taken together, these data provide further evidence against the assumption held previously by the Bobaths (1969, 1978), namely that activity increases spasticity and should therefore be limited. They support similar findings (e.g. Badics *et al.,* 2002; Morris *et al.,* 2004, Bütefisch *et al.,* 1995; Bourbonnais *et al.*, 2002) which demonstrate the lack of impact of physical activity on spasticity. Although it is possible that RTPM in general (and spasticity in particular) may have increased during therapy sessions, the resting and stretching intervals may have been sufficient to counteract this effect and prevent any adverse effects in the longer term.

5.2.6 OTHER EFFECTS

Some participants reported effects that would not have been detected directly by the assessment battery.
Interestingly, two participants in the EG and one in the CG reported improvements in gait. Similar findings were reported in an observational study by Bakheit *et al.* (2002). It is plausible that in people with associated reactions during walking, BTX-A injected into the UL would increase its number of degrees of freedom, rendering it easier to make fine adaptations to perturbations whilst maintaining postural control. A different explanation could be based on sensory changes in the affected limb. A number of participants reported that they had become more aware of their affected arm following the intervention. It is possible that increased attention and/ or tactile and proprioceptive stimulation associated with various therapeutic procedures

during the programme may have facilitated neuroplastic changes in the somatosensory cortex representing the affected limb (Hummelsheim *et al.,* 1995). However, one would not expect these to transfer to an improvement in balance and gait without specific practice. There is a possibility that the intervention may have brought about a more general awareness of the affected side as a whole, which may have facilitated weight bearing on the lower limb. A different explanation again could be associated with general self-efficacy, which the research physiotherapist may have enhanced and which may have encouraged participants to increase the involvement of their affected side. The effects of BTX-A on gait could be further explored in future studies, using 3D motion analysis instrumentation.

Increased sensation in the affected UL was reported by three participants in the CG and two in the EG, some of whom had not experienced any sensation in their arm since stroke onset. As explained above, it is quite plausible that the stretching, donning, doffing as well as the pressure of the upper limb splint all generated increased somatosensory stimulation and perhaps circulation in the CG. Participant P05 in the CG appeared to have become more "aware" of his arm and tried to involve it more in activity, possibly out of concern of the effects of disuse. This suggests that, in some people, sensory stimulation *per se* may act as a cue to remind them of the presence of the affected limb. Although this would not provide specific information on how to use this limb in functional tasks (in contrast to the EG, where participants were trained specifically), it is possible that an increased awareness of the affected limb could motivate some people to explore its potential in action.

Four participants in the CG reported an increased sense of relaxation in their affected arm (P02, P09, P14). In participants P05 and P14, this appeared to have made it easier to care for their hand (App. 4.10). "Relaxation" of the affected limb may be an important treatment goal for some patients and it would be worthwhile to explore how this could be assessed more formally, e.g. by means of a VAS.

An interesting comment was made by participant P13 in the EG, who said that he had begun to involve his affected arm again in gesturing.

5.2.7 ADVERSE EVENTS

Adverse events were quite common during the study (table 4.5). The percentage of adverse events in this study was much higher than that in comparable investigations, e.g. Brashear *et al.* (2002) reported 48% of their sample having experienced adverse events, whilst Hesse *et al.* (1998) simply noted an absence of adverse events altogether.

Fatigue and transient upper limb pain were common and occurred at a similar frequency in both groups. These symptoms may have been due to the comparatively high intensity of training, but this remains speculative because of the lack of data in other studies. Although Bakheit *et al.* (2001) also listed fatigue as a common finding, this in itself is known to be a general problem after stroke (Staub and Carota, 2005). Unfortunately, there were no data to indicate whether fatigue levels changed as a result of taking part in the programme. From the case notes provided by the research physiotherapist at the end of the trial, it emerged that most participants had maintained their normal daily routine and added the therapy programme onto what was already a busy schedule in many cases. Comments from some participants suggested that transport and logistics tended to be the culprits rather than the actual content of the programme itself. Although the programme was not expected to cause fatigue on the basis of biomechanical or cardiorespiratory factors, the demand it placed on cognitive abilities may have played an important role. Especially during the last week, with random and variable practice, contextual interference was high and it is plausible that this placed a considerable strain on participant's information processing skills, which may already have been compromised as a result of the stroke.

The difference in incidence of adverse events between studies may also be related to the intensity and quality of the contact between participants and health care professional. From informal comments made by the participants in the current study, it was clear that their rapport with the research physiotherapist was excellent and this may have evoked more (and perhaps more confidential) information than in similar investigations that were not accompanied by such intensive therapy.

Three serious, non-treatment related adverse events occurred during the study: a bilateral clavicula fracture in participant P11, sustained during DIY, an undiagnosed

neck and arm injury in participant P13, also sustained through DIY and collapse due to high temperatures in participant P05. Apart from these, all other adverse events were considered to be non-serious.

5.2.8 EXPLAINING CHANGES IN OUTCOMES

Having summarised the effects of the skill acquisition programme, it is time to explore possible explanations for these findings. Any differences between the two groups may have been mediated by biomechanical, as well as neuroplastic factors. To begin with biomechanical variables, the differences between the two groups in terms of arm function and ADL could not be explained by changes in elbow flexor spasticity, non-neural factors contributing to RTPM or grip force, as any changes in these variables were not significantly different between the two groups in any of the study phases. Force production in other muscle groups may have changed, but this was not assessed. Possibly, the intensity and duration of this programme was insufficient to expect any lasting changes in force production, but there is little relevant research: studies on strength training after stroke have concentrated on the lower limb (see Morris *et al.,* 2004 for a review). Findings from two studies involving upper limb strength training were not applicable as they pertained to sub-acute patients (Bütefish *et al.* 1995 and Winstein *et al.* 2004). Curiously, one study testing the effects of strength training with people in the chronic stage omitted a measure of strength in their outcomes (Thielman *et al.* 2004). In a RCT with chronic stroke patients, Bourbonnais *et al.* (2002) found no significant improvements in grip force or upper limb function following an isometric strengthening programme, despite some improvements in other UL strength measures. Improvements in passive and active ROM could also have played a role, but again these were not included in the assessment battery. The stretching procedure may have reduced any soft tissue contractures, but this intervention was applied to both groups. In fact, it would be reasonable to expect passive ROM to have improved more in the CG following the splinting programme, but even if this were the case, it apparently did not carry over into functional activity. Altogether, it is unlikely that the differences observed between the two groups could have been mediated by biomechanical factors. Instead, neuroplastic changes are more likely candidates.

In the absence of information on brain activity in this study, it is not possible to postulate which neuroplastic changes may have been involved and therefore the following explanations remain speculative. The key principle of the skill acquisition programme was that it encouraged participants to engage in active problem-solving, whether through overt or covert practice. This may have facilitated changes in established neural networks that were used routinely and automatically, by involving the prefrontal cortex, which plays an important role in action planning (Kolb and Whishaw, 2003). Additionally, the premotor area may have been activated, which is involved the selection and direction of movement sequences (Kolb and Whishaw, 2003). Indeed, a number of participants commented that they had to "think" about new ways of using their affected arm. These findings are consistent with those reported by Dettmers *et al.* (1997, cited in Ploughman 2002), who found increased activation of executive cortical areas in tasks that would be considered to be automatic in non-impaired people. The physiotherapist in this study also noted that some participants actively prevented their non-affected hand from participating (e.g. by sitting on it). This would suggest that they were either inhibiting former habits or that the effort of involving the affected UL additionally activated ipsilateral pathways and/ or the intact hemisphere (e.g. see Turton *et al.,* 1996; Cramer *et al.,* 1997). The finding that, in some participants, improvements in upper limb function and ADL were still apparent several weeks after the intervention programme had finished, suggests that any neuroplastic changes were relatively durable and well-beyond the duration of any rapid, short term memory changes associated with mere performance. Thus, unmasking of latent synapses may have occurred, explaining short-term improvements, with long-term potentiation and possibly collateral sprouting mediating long-term changes (Celnik and Cohen, 2000). However, as explained above, these explanations are speculative and further work using appropriate neuroimaging techniques is required to obtain further insight into durable, functional neuroplastic processes associated with task-orientated practice in chronic stroke.

5.3 STUDY LIMITATIONS

5.3.1 DESIGN

The current trial, a randomised, placebo-controlled feasibility study, enabled the differential effect of additional functional UL training to be compared with a passive treatment component (i.e. the placebo control condition) following the injection of BTX-A. The study was not designed to compare skill acquisition combined with BTX-A with BTX-A alone, as this comparison would have been confounded by a number of factors, particularly differences in therapy time and soft tissue mobilisation.

Another limitation of the current design was that it did not enable the relative efficacy of the two main learning strategies, used within the skill acquisition programme (i.e. mental and physical practice), to be differentiated. In an early stage of designing the study, a two-by two-factorial design had been considered which would have enabled this to be investigated, but this idea was dropped because of the expected limitations of the sample size. As already indicated in Chapters One, further research is required to determine the relative efficacy of different learning strategies (e.g. physical practice with different schedules for practice and feedback, mental practice) in stroke rehabilitation.

Baseline had been tested on a single occasion only, the main reason being to avoid overload associated with repeated assessments. It is acknowledged that the methodology would have been more robust had at least a double baseline been used, but given that all participants were at least 1.4 years post stroke, their condition was estimated to be sufficiently stable (e.g. Woldag and Hummelsheim 2002; Page 2000, 2005).

Follow-up was limited to one 13-week BTX-A cycle, which is a relatively short period of time. Clearly, it would have been valuable if follow-up could have been extended to explore longer term effects, but the ethical and logistic complications involved were considered to be prohibitive, given the available resources. However, it would be interesting in future to study longer term effects of task-orientated practice on

ADL and arm function, as well as any subsequent requirements for BTX-A treatment.

5.3.2 STUDY SAMPLE

The cardinal limitation of this study was its restricted sample size (the reasons for which were set out in section 5.2.1) and there is no doubt that the study was underpowered. Associated with this is the risk of a Type II error, i.e. to incorrectly accept the null hypothesis (Howell, 1992). Whilst acknowledging the need to limit the experiment-wise error rate and keep the Type I error in check (Field, 2000), the Type II error in this study may have been inflated through the combination of the sample size, non-parametric statistics and the Bonferroni correction. There is debate in the literature regarding the need for the Bonferroni correction in studies with multiple comparisons. Bland and Altman (1995) - whilst warning against including too many statistical tests in any one study - considered the Bonferroni correction to be inappropriate in cases where tests were highly correlated (which applied to the current study with its repeated measures), as it is highly conservative. Whilst acknowledging the merit of the Bonferroni correction in a limited number of scenarios, Perneger (1998) argued that it was at best unwarranted and at worst detrimental to sound interpretation of statistical findings related to specific hypotheses. Further debate on the strengths, drawbacks and alternatives for the Bonferroni correction can be found in Feise (2002).

Taken together, it is clear that the study needs to be replicated in a future multi-centre trial, for which Appendix 5.1 suggests a sample size estimation.

Other important limitations were already highlighted in section 5.2.2. In many ways, the sample was self-selecting in that those with low mood, motivation or poor health would probably not have wished to participate. The sample was also selective in that, despite severe impairments and activity limitations, most participants still had some active function in their affected UL. Thereby, they represented only a subset of those requiring BTX-A for UL spasticity, which also comprises a considerable proportion of people with no active UL function at all. These people had not been represented but would warrant a separate investigation with a different intervention and appropriately targeted outcome measures. A comprehensive epidemiological

study, charting the characteristics and treatment needs of people requiring BTX-A for UL spasticity would be useful for health service planning and financing purposes. Finally, most participants were male, while the three women were all randomised into the CG. This implied that the effects of gender on outcomes could not be explored. Altogether, these characteristics highlight the specificity of the sample and caution that the results from this study should not be generalised prior to replication with a more representative stroke population.

Diagnostic information was limited in some cases (particularly with regards to participants who had a stroke several years ago), which restricted the analysis of the effects of lesion side, site and severity on skill acquisition. Further research into this topic is essential in order to develop our understanding of the processes involved in recovery and relearning following a stroke.

5.3.3 INTERVENTION

Content

Following recommendations from the general stroke literature to investigate single, well-described interventions (Platz *et al.,* 1999, Woldag and Hummelsheim, 2002), the content of the programme had been restricted to one type of therapeutic input only. Although the benefit of this strategy is clear, its drawbacks also need to be recognised. One could argue that this approach is not congruent with clinical practice, where different treatment modalities are often combined. Additionally, Wade (2001) argued that a reductionistic approach to efficacy research, i.e. attempting to establish the effects of individual treatment components, administered in isolation, could lead to erroneous conclusions. The effects of isolated interventions might be too small to detect, whereas if delivered together, their interaction could have a significant impact. Wade suggested that the erroneous conclusion that a rehabilitation strategy was ineffective when investigated in isolation, be labelled as a Type III error. He used treatment with botulinum toxin as an example, stating:

> "*no researcher has even considered investigating botulinum toxin in isolation. Every study has set the use of botulinum toxin in the context of active therapy*" (p. 3).

The evidence from the review in section 1.3 would call this statement into question however, with more than 20% of the studies failing to report any concurrent intervention. Additionally, the difference between what is provided in a research setting and what is available in actual clinical practice needs to be considered. Hence, although Wade's argument is valid and thought-provoking, the current status of neurological rehabilitation as the "black box of treatment" (Ballinger et al., 1999, Pomeroy and Tallis, 2002b) renders it necessary to begin by establishing the effects of single, well-defined interventions. Upon this foundation, further research will then be required to assess the effects of different combinations of interventions.

With regards to the content of the skill acquisition programme, the number of UL activities had been limited to four categories (yielding at least 240 variations in total), in addition to one optional task. This selection had been based on a pragmatic approach, involving informal pilot work with a similar group of people (Appendix 3.6). Inevitably however, the selection only represented a subset of ADLs, which inevitably would have been biased by the views of the participants involved in the pilot work. This approach could have been strengthened through more formal qualitative research, e.g. using focus groups, but this was beyond the scope of the present study. This purely pragmatic approach could also be criticised for lacking in theoretical rationale. A theoretical approach to task selection was employed by Platz *et al.* (2001) in his Arm Ability Training. On the basis of factor analysis of motor performance of healthy subjects, eight different tasks were chosen which together were thought to represent a number of fundamental, independent arm abilities. However interesting, this approach could be questioned, particularly with regards to the ecological validity of its content. It is clear that further work is required to establish the content of therapy programmes for people with specific impairments and activity limitations on the basis of qualitative, patient-centred research as well as a sound theoretical rationale.

Strengthening exercises *per se* did not feature in the current programme; instead, strength was trained implicitly by gradually increasing the biomechanical load of the functional tasks. Given the low level of grip force of the study sample, it would be valuable to assess the efficacy of additional strengthening exercises in future. However, a study by Bourbonnais *et al.* (2002) failed to show improvements in hand

grip strength following a six-week training programme for people in the chronic stage after stroke. A small scale study by Thielman *et al.* (2004), comparing the effects of task-related training and progressive resistive exercise in the chronic stage after stroke suggested that task-related training yielded more benefit in terms of upper limb function than mere strength training. In an interesting study comparing the effects of strength training and task-related training (which bore resemblance with the skill acquisition programme in the current study) in acute stroke, Winstein *et al.* (2004) found that the task-related group improved more on upper limb function measures and even outperformed the strength training group in terms of UL force parameters at nine-month follow-up. The authors explained this finding by suggesting that task-related training may provide a more meaningful context for strength training than strength training *per se*. Together, these studies further highlight the importance of occupational embedding of task practice.

Mental practice (MP) was an integral part of the therapy programme and provided an opportunity to covertly rehearse the tasks that were carried out overtly. The procedure for MP had been standardised and instructions were read out from a script by the research physiotherapist in order to avoid confounding variables associated with differences in information input between participants. In clinical practice however, a therapist would be inclined to tailor the instructions to the needs of the individual and it is plausible that the effectiveness of MP in this study was less than optimal.

The amount and scheduling of MP and physical practice was different from most other studies in stroke rehabilitation. The studies by Page (2000) and Page *et al.* (2005) provided a total of 30 minutes of MP per session, provided as a separate component. The amount of mental practice in the current study was considerably less (i.e. approximately 10 minutes per session), which may have limited its efficacy. Additionally, participants in the current study were required to switch quickly between the two different modes of practice, as they were interspersed. The rationale for this schedule was that this was thought to promote carry-over into ADL, where one rarely gets an opportunity to engage in covert practice for an extended period of time before taking action. Interestingly, some participants in the current study mentioned that they found "thinking about" an activity before doing it to be

helpful. The research physiotherapist also noted on a number of occasions that when a physical practice trial had been preceded by MP, it appeared to be performed better than without it[4], but this would need to be tested more formally. The observation, however, fits in with Jeannerod's (2005) interpretation of overt action incorporating a covert stage, which facilitates the processes involved in the actual activity.

Taken together, mental practice in stroke rehabilitation is a relatively new line of research and although its potential is widely recognised, much further work is required. To begin with, there is a paucity of evidence regarding the suitability of MP for people with specific neurological impairments. Further work is also required to establish optimal content, organisation, frequency and duration of MP in relation to PP. It could be envisaged that, in the cognitive stage of learning, it might be more effective to practice MP separately until the basics of this skill are understood. With increasing proficiency, MP could be integrated with physical practice as this could be more effective in terms of transfer to ADL, but this would need to be investigated.

Duration, frequency and intensity

For each participant, the intervention programme offered 15, 1-hour sessions distributed over a three-week period. Given the severity and chronicity of the upper limb problems encountered in this study, it would have been unrealistic to expect major changes over such a relatively short period of time, but a longer treatment cycle had been deemed to be too burdensome. However, the results indicated that this short but intensive programme did facilitate improvements in some participants in the EG. Whereas changes in ADL (i.e. SIS-5) were still apparent nine weeks after the therapy programme had finished, improvements in hand function (i.e. ARAT and SIS-7) were more short-term. In order to facilitate longer-term changes in upper limb function, an alternative programme could be piloted whereby the duration of the programme would be extended, whilst contact with the therapist would progressively

[4] Interestingly, from the pilot study, reported in Appendix 3.6, there was some indication that participants applied the principle of covert rehearsal to tasks which were not part of the therapy programme (i.e. they were of a different category or new altogether). This challenges the specificity of learning principle in that covert rehearsal would constitute a more generic skill which could be applied to different categories of skills, but this would require further research.

be reduced and supplemented with a home programme and exercise diary. This could be more effective in terms of enhancing carry-over, as it would provide the participant with more opportunity for independent practice in their own environment. In addition to being more cost effective, it would also avoid fatigue associated with an intensive schedule and frequent travel.

In the EG, the transition from Week 2 (with random and constant practice) to Week 3 (with random and variable practice) appeared to be quite challenging. This may be explained by the considerable increase in contextual interference, as well as the fact that Week 3 provided limited opportunities for repetition. Some participants indicated they would have preferred to have had more opportunity to practice each task. A more extended phase of random and variable practice would have been useful to consolidate learning and facilitate transfer into ADL, which is characterised by this type of organisation.

Single Therapist

In order to avoid inter-therapist variation in administering the therapeutic input and evaluating the COPM, a single therapist had provided all treatment sessions. However, this aspect could also be interpreted as a limitation of the study, as any changes could be associated with the personal style of the therapist. This could have been circumvented by involving a number of therapists in future work. In fact, at the time of writing, the therapeutic programme - in slightly amended form – is administered by four therapists in a multi-centre trial evaluating the efficacy of BTX-A in UL spasticity after stroke the north-east of England (van Wijck et al., 2006[b]).

Timing with respect to BTX-A

The intervention commenced between four-five days following the BTX-A injection. With the effects of the toxin normally being at their peak between two and six weeks (Simpson *et al.,* 1996), it was reasoned that starting additional treatment in the first week would make most of this window of opportunity and possibly extend the period over which the toxin would normally be effective. Starting early would also mean that participants would exit the programme while the toxin was still active rather than in decline, which would be more likely to enhance their motivation to carry on using their affected arm. However, it could be argued that it would be more effective to

postpone the additional treatment until the BTX-A effects were well established, but there did not appear to be any evidence to support one strategy or the other. Further work to identify the best window of opportunity would be valuable in order to achieve an optimum treatment effect.

5.3.4 OUTCOME ASSESSMENT

General Considerations

The assessment battery had been designed to represent all three domains of the WHO ICF. With its focus on spasticity and activity however, the study was inevitably biased towards impairments and activity limitations – as is most of the literature on BTX-A (sections 1.3 and 1.4). Furthermore, in order to avoid assessment overload, only selected aspects of these two domains could be addressed. For example, although the research physiotherapist assessed joint motion, muscle strength and sensation, they were not considered to be the primary goals of the intervention and therefore not included in the assessment battery. Taken together, the current study only allowed a narrow – and inevitably partial - view of any changes that occurred.

With respect to participation restrictions, data from the COPM and the SIS confirmed work from other authors that concerns about these issues are common and often neglected (Lai *et al.* 2002; Dekker *et al.,* 1995; Wyller *et al.*, 1997). Having come to terms with the biomedical aftermath in the chronic stage after stroke, re-engagement with society may become a more important than "mere" deficits. For rehabilitation services to make a meaningful contribution to people's adjustment and re-integration into society, further research at the level of participation restriction is required urgently.

ARAT

The limitations of the ARAT, experienced during the current study, were very similar to those described in section 3.7.3 and will therefore not be repeated here.

Additionally, the restricted employment of user-centred space of the ARAT (figure 5.1) highlighted its limited content validity, while the ecological validity of the ARAT was considered to be restricted, as will be discussed in section 5.6.3. Taken together, these issues raised the question whether there would have been an alternative, more appropriate UL function tool for this study, but a review (Platz et

al., 2005) clearly demonstrated the psychometric properties and functional relevance of the ARAT to be superior to those of other UL function tests. An interesting additional measure would have been the Motor Activity Log (see Uswatte *et al.*, 2005), which would yield insight into the actual usage of the affected limb in a person's daily life. Perhaps supplemented with biomechanical measures of activity (e.g. accelerometers), the use of this instrument could be considered for future work.

COPM

For logistic and other practical reasons, the COPM was not assessed at Week 7. With the benefit of hindsight, it was realised that this constituted an important limitation, especially given the changes in ARAT at that time. Additionally, the period between Weeks 4 and 13 was relatively long and an interim COPM data point would have been of value.

It is important to emphasise that the COPM is a self-report measure, designed to explore the person's view on personally relevant issues. As with any self-report measure, discrepancies may exist between perceived and actual performance (Baranowski, 1988). In order to be able to compare and contrast these, it would be of interest, where meaningful and practicable, to additionally assess actual performance. This would only serve the purpose of comparing within-subject performance, as the COPM is not norm-referenced, given the notion that occupational performance is modelled as individually determined (Law *et al.*, 1998). For this purpose, the Assessment of Motor and Process Skills (AMPS, Fisher 1997) could be useful as an addition to the assessment battery, as it uses standardised observation and rating of patient-selected ADLs and has been researched extensively. Unfortunately, usage of this tool required resources that were not available for this study, but future studies should consider the AMPS, which could strengthen the patient-centred dimension of the assessment battery.

Spasticity and RTPM measures

The main limitations of the DATA system have already been discussed in Chapter Two and these will not be repeated. An additional limitation that emerged during this study was that - unknown to the investigator - the operating range of the system had been reduced during a factory calibration that took place between the previous study and the current one. This limited the registration of RTPM in 12% of the trials,

but since data beyond 75% of maximum angular displacement (after which RTPM tended to level off) were not used for the analysis, this did not constitute a problem: in the trials that had been affected, there was no significant difference in RTPM measured before or after the cut-off (p=0.10).

Unsurprisingly, the Ashworth scale continued to suffer from the limitations that were already discussed in some depth in section 3.7.3 and these will not be repeated here.

Stroke Impact Scale (SIS)

The SIS yielded a relatively comprehensive picture in terms of changes in the three domains of the ICF over the course of the study. However, an important omission was the absence of any item dedicated to pain or fatigue, which are both common following stroke (Staub and Carota, 2005). Although the study sample had been selected on the basis of the absence of upper limb pain, it emerged that the majority of participants did experience some pain during the study and it would have been valuable if this could have been monitored.

Grip Force

The protocol for measuring grip force was limited to maximum voluntary contraction only. Although its correlation with arm function is high (Boissy *et al.*, 1999), dynamic measures (e.g. duration of sustained grip force or time to peak force) would have provided more insight into functional control problems concerning grip force. In further studies, it is recommended that dynamic grip force measurements be taken where possible.

Other outcomes

As indicated earlier, several changes were reported that fell out with the spotlight of the assessment battery; notably pain, sensation, relaxation and hand care. A more formal evaluation, particularly of sensation and propioception would have been helpful for exploring its impact on skill acquisition, but any further tests would have added to the already considerable burden of assessment, which was not thought to be acceptable.

Visual Movement Imagery

The Visual Movement Imagery Questionnaire (VMIQ) was not used as an outcome measure in order to avoid assessment overload, but it would have been of interest as there is evidence suggesting that movement imagery ability may improve following practice (Hall and Martin, 1997). Some participants in the EG reported that they found mental practice (which involved movement imagery) difficult at first, but increasingly easy to use and it would have been of interest to assess whether their ability to use this technique had changed as a result of the training.

The VMIQ was developed with a sample of non-impaired students (Isaac *et al.* 1986) and did not include any stroke-specific items. In fact, many of its items (e.g. "jumping off a high wall" and "swinging on a rope") were clearly inappropriate for the participants in this study (and probably for most people after stroke) and therefore the validity of the information emerging from the VMIQ was questionable. In future studies, other methods for testing the ability to engage in mental practice could be explored, e.g. mental chronicity (Dijkerman *et al.*, 2004).

5.4 SOURCES OF ERROR

5.4.1 STUDY SAMPLE

Demographic variables, diagnosis and BTX-A treatment

The sample in this study was heterogeneous in terms of age, time post stroke, stroke type and lesion site, as well as BTX-A treatment. Although there were no significant differences between the two groups with respect to age or time after stroke, each of these factors may have contributed to variation in the outcomes. With respect to lesion site, Shelton and Reding (2001) observed that recovery of selective UL movement was greatest in patients with small lesions of the posterior limb of the internal capsule only, and poorest in those with a lesion involving the posterior limb of the internal capsule as well as the corona radiata, basal ganglia or thalamus. Additionally, the side of the lesion may have influenced the outcomes, e.g. Harrington (1991) and Rushworth *et al.* (1997, 1998) pointed out the specific role of the left hemisphere in attention and motor planning. In this study, four participants out of five in the EG had right hemispheric lesions, compared to three

out of seven in the CG. The data from this study suggested that the EG found it considerably more difficult to engage in movement imagery than the CG, although there were no significant differences between their scores (table 4.1). This is congruent with what is understood to be an important role of the right cerebral hemisphere in general in the spatial organisation of movement and the mental rotation of shapes, with the posterior parietal lobe in particular playing an important role in the control of visuospatial functions in user-centred space (Kolb and Whishaw, 2003). Difficulties with engaging in movement imagery may have affected the ability to use mental practice, which in turn may have diminished the potential impact of the skill acquisition programme (Eton *et al.,* 1998). Further studies where stroke site and severity are controlled or accounted for are required to explore the impact of different brain lesions on movement imagery and mental practice ability.

As indicated in tables 4.44[a,b], there was also considerable variation between participants in terms of BTX-A treatment. Although there was no significant difference between the two groups in terms of total dosage, differences between injection sites and dosage per site could have influenced the outcomes, as the effects of BTX-A are site- as well as dose dependent (Simpson *et al.*, 1996; Childers *et al.*, 2004).

Taken together, it is clear that this study requires to be replicated with larger and more homogeneous groups of patients in terms of time after stroke, lesion side, site and severity as well as BTX-A treatment, which will require a multi-centre trial.

Sensorimotor characteristics

Information from the formal baseline characteristics, as well as the research physiotherapist's case notes (not included here), indicated that participants varied considerably in terms of upper limb range of movement, strength, sensation, level of distal control as well as resistance to passive movement in joints other than the elbow. Clearly, each of these variables could have influenced the treatment outcomes and had they been assessed and taken into account, their impact on the efficacy of the interventions could have been explored, but unfortunately, this was not feasible in the current study.

Contralateral Neglect

In this study, one participant in each group showed evidence of neglect, but since there were missing data in both groups, there was insufficient information to ascertain whether contralateral neglect could have had an influence on the outcomes. There is some evidence in the literature that upper limb rehabilitation may have differential effects, depending on the presence of neglect (Feys *et al.* 1998; van der Lee *et al.,* 1999), but this has not been widely researched. Further work is required to explore the impact of different forms of neglect on skill acquisition.

Pain

The eligibility criteria had been selected to exclude people with joint pain in order to protect those randomised into the EG from potentially aggravating this condition. During baseline assessment, a number of participants mentioned some degree of UL discomfort but had difficulty distinguishing this from "tightness", or an "awareness" of the UL. In none of the cases was this aggravated by UL activity during initial assessment. It was therefore surprising to find that most participants - in both groups - reported some degree of transient UL pain at some point during the therapy programme. It is quite possible that some participants, in their enthusiasm to take part, chose to refrain from disclosing the fact that they did have some UL pain, as they had been advised that this was an exclusion criterion. Alternatively, they may have been so habituated to the presence of some form of pain that they may not have thought to mention it. Transient discomfort or pain may have been induced by the therapeutic input by placing stress and strain on soft tissues, which those who had not received any UL therapy for some time, may not have been accustomed to. However, considering the reasons for absence during the study (table 4.6), the presence of temporary UL pain did not seem to have been a factor. In future studies, it is recommended that pain be assessed with a more sensitive tool and monitored throughout.

Cognition

Although all participants passed the criterion for the Mini Mental State Examination (Galasko *et al.,* 1990), it became apparent that some experienced attention and/ or memory problems, which became manifest as difficulties with concentration and/ or

multi-stage instructions in the EG. Looking at the content of the MMSE more closely, it is clear that this test is not sufficiently specific to detect these types of deficits. Therefore, it is plausible that some of the results may have been affected by mild cognitive impairments, especially the self-report measures, some of which were quite long (i.e. the SIS and VMIQ) or complex (i.e. the COPM).

Communication

All participants passed the criterion for communication, but subtle difficulties with comprehension may have influenced the ease with which participants in the EG were able to understand the verbal instructions and feedback. Additionally, outcomes on the COPM or SIS could have been affected by comprehension deficits. Again, more specific and detailed screening for potential communication deficits would be helpful to control or account for these potentially confounding variables in future.

Movement imagery ability

The mental practice technique, used in the skill acquisition programme, relied on participants' ability to engage in movement imagery. In the EG, this ranged from severely impaired to normal (table .4.1) and it is plausible that this between-subject variation was responsible for some of the differences in the results in the EG. An interesting case was participant P13, who sustained a right MCA stroke. When this gentleman attempted to visualise movement, he reported to the therapist that he only saw "black"[5] and that he would try and focus on the instructions that were read out instead. Thus, this gentleman may have substituted visual for auditory processing, possibly making use of other neural networks that had been preserved. This case raises the issue that, even if the input for mental practice be standardised, the way in which it is processed may vary. A cardinal weakness of mental practice is that it cannot be monitored. To some extent, functional neuro-imaging techniques would be useful as they would indicate which brain areas were active during mental practice – although they would not yield information on the specific cognitive processes involved.

[5] This gentleman also mentioned that he had not had any dreams since his stroke, which used to be quite lively in terms of visual content.

There was no information on participants' previous experience with MP and it is likely that those who had used it before were more proficient at it and may have derived more benefit from the intervention.

Transport facilities

Regrettably, due to resource restrictions, it had not been possible to provide transport for participants to and from the clinic. Some participants drove themselves but reported that this was quite tiring, others were dependent on carers, whereas those using the ambulance often took a long time to travel. Yet again, others had no transport issues at all. Taken together, the mode of transport may have been a confounding variable in this study through affecting fatigue. Therefore, future investigations should procure sufficient funds to provide transport for their participants.

5.4.2 INTERVENTION

Content

The therapeutic input had been standardised as far as this was practicable. However, since participants' individual characteristics had to be accommodated, some factors were inevitably left open to variation, as will be discussed below for each component of the intervention.

The stretching programme, which was common to both groups, stipulated the muscle groups, direction and duration of each procedure. However, differences occurred between participants in terms of handling, the speed at which tissues were elongated and the duration of the period in which participants remained at maximum comfortable range of movement. Additionally, some amendments had to be made for people with different spasticity patterns, in order to adhere to the principle of stretching the muscles that had been treated with BTX-A. Whilst acknowledging these inter-subject differences and their potential impact as confounding variables, it was accepted that it was not feasible to standardise the stretching component of the programme any further.

In the splinting protocol for the CG, the target position of the limb, maximum air pressure and overall treatment time had been specified, but more subtle differences in donning and doffing the splint were inevitable, as it was important to ensure that participants remained comfortable. One participant (P14) was provided with a fore-arm splint, in order to avoid increasing tone in his elbow extensors. In cases where it took longer to don the splint (e.g. because of severe spasticity), the amount of time participants remained in the end position would have been reduced and this may have diminished the potential impact of the intervention on tone and range of movement.

In the skill acquisition programme for the EG, the following parameters had been standardised: the sequence of demonstration procedures, type of practice, number and category of the tasks, number and order of repetitions, mental practice instructions as well as the frequency of feedback. However, within the confines of these invariants, adaptations had to be made to allow for individual differences in range of movement, strength and coordination. Therefore, the following parameters had not been standardised: physical load and specifications of the individual objects, reaching distance and the precise amount and content of the feedback. All of these factors could have confounded the results, but given the heterogeneity of the EG, it was not possible to standardise any further. Studies using a similar intervention (e.g. Winstein *et al.*, 2004), also reported that only certain parameters could be standardised but that the actual input had to be fine-tuned according to the needs of each individual patient.

Although an attempt to standardise therapeutic input has been advocated for the purpose of research (deJong *et al,*. 2004), such a formulaic approach could also be criticised as being unrepresentative of clinical practice, where therapists endeavour to deliver tailor-made treatment. Thus, the study sought to find an optimal balance between individually targeted and standardised therapeutic input. Inevitably, the result was a compromise. Within the confines of the invariants however, the research physiotherapist indicated there was sufficient opportunity to adapt the programme to the needs of each individual participant. The protocol was generally adhered to; all patients were able to perform each task at least to some extent. Alterations, which were recorded on the daily exercise sheet for each participant, occurred when the task was considered to be too difficult or too easy. In these

cases, the therapist adjusted the parameters of the task, ensuring that it remained within the same category of activity.

With regards to MP, instructions had been standardised and were read out by the research physiotherapist, as this was more practicable. In contrast, other studies (Page, 2000; Page *et al.,* 2001, 2005) provided instructions to guide MP through a recorded tape. In the current study, variations in speech volume, speed and pitch may all have affected participants' comprehension of the information as well as their level of motivation. In order to avoid these potentially confounding factors in future studies, recorded instructions should be used rather than scripts wherever this is practicable.

Therapy environment

The therapy environment for this study had been a physiotherapy gymnasium, with a curtain around the treatment area. This had been chosen in order to replicate conditions in normal clinical practice. However, the research physiotherapist reported that noise levels seemed to interfere at times with mental practice and with physical practice as well, which may have diminished the results.

Fatigue

As indicated before, fatigue was a common adverse effect (table 4.5), which may have affected performance and perhaps also long term retention. The treatment schedule was quite intensive and although one participant expressed a preference for a more intermittent schedule, none of the others reported it to have been problematic. However, as already indicated earlier, it appeared that many participants had not adapted their daily programmes when they entered the study. To reduce fatigue in similar trials in future, participants would need to be advised more explicitly about the treatment intensity.

Independent practice

In order to avoid potential overload, all participants in the study had been advised (Appendix 3.3) not to change any activities outside therapy that involved their affected UL. Additionally, in order to avoid any confounding factors associated with home exercise, all therapeutic input had been delivered through the same

physiotherapist. However, in both groups there were participants who "confessed" that they had explored different ways of using their affected arm, as they were curious to find out what they could achieve. It is likely that this additional activity may have influenced the results, either in a positive or negative way, depending on the type and intensity of practice. For future work, it is probably more realistic to assume that at least some people will try to use their affected arm, especially following ADL-orientated treatment, and therefore it would be recommended to guide rather than prohibit additional practice through a home-based exercise programme.

Participant-therapist interaction

At follow-up appointments, spontaneous comments from participants about the research physiotherapist were invariably very positive. Some commented that they had been given expert therapy and had appreciated the opportunity to discuss their issues. The fact that there were no drop-outs due to treatment-related factors – especially in the control group – together with the high attendance levels suggests that the therapeutic input was valued highly. This could be an important factor in explaining the considerable increases in COPM-Satisfaction scores in both groups, which were not always reflected in the corresponding COPM-P scores. As in normal clinical practice, participants were not only treated but also listened to and given advice. It is possible that more therapeutic communication took place in the CG, where participants rested in their splint, compared to the EG, where the focus was on activity. Additionally, 10 out of the 12 participants were given advice or were referred onto other services during or after the intervention for non-UL related issues such as employment, general health, orthotics and communication. However, since these issues had been excluded from the COPM analysis, they would not have influenced the outcomes.

Hand splints

In this study, only one participant used a hand splint, who had been advised to continue her normal schedule. However, it emerged at the end of the therapy programme that this participant had not used the splint for a week, as she considered it unnecessary. However, at follow-up in Week 13, this participant mentioned that her hand felt "much tighter" than at Week 7. Hence, an alteration in

splint usage may have confounded the results for this individual. In future studies, where relevant and practicable, a hand splint diary could be employed so that its use may be monitored and controlled where necessary.

5.4.3 OUTCOME ASSESSMENT

General considerations

Although the assessments were scheduled to occur at fixed points in time, adaptations were necessary to allow for personal circumstances in some cases. E.g. due to differences in BTX-A treatment cycle duration, participant P10 was re-assessed at Week 10, whilst P13 was scheduled for Week 15. Earlier assessments may have yielded more positive outcomes than later ones, with the neurotoxin still having some impact. However, since the study did not intend to interfere with the clinical procedures involved in the BTX-A treatment, these potentially confounding factors were unavoidable.

ARAT

Sources of error associated with the ARAT were already discussed in section 3.7.3 and those points will not be repeated here. One further point emerged in this study, namely that the ARAT appeared to assess potential upper limb function - which was not necessarily the same as actual function. Some participants expressed surprise after having completed the ARAT, as they had not realised they were able to perform some of the tasks. This matches an observation by Page *et al.* (2005), which highlighted a stark contrast between ARAT scores (which indicated only moderate impairment) and actual use of the affected arm in ADL on the Motor Activity Log (which was negilible). This would suggest that ARAT scores may overestimate actual UL function, which may be masked by learned non-use.

COPM

At baseline, the COPM required participants to identify and prioritise current occupational issues and score up to five of the most important ones on two different dimensions, each consisting of a 10-point scale. This procedure, which could take up to 30 minutes per participant, required relatively complex and sustained cognitive and executive functioning. Although participants in the study had generally good

cognition and communication skills, some expressed considerable difficulty with this task. Law *et al.* (1998) stated that the COPM may not be appropriate for people with cognitive impairments, and that assistance from their carers or members of the family could be considered, whom a number of studies have indicated to be reasonable "substitutes". However, for this tool to be used with people with more pronounced cognitive and/ or communication deficits, further validation work would be required.

Finally, the COPM was evaluated by the research physiotherapist, which may have biased participants' responses. This could have been avoided by including an independent assessor, but although this was considered, this option was rejected as it would have introduced further logistical and resource complications.

Spasticity and RTPM Measures

Most of the sources of error associated with the DATA system were already discussed in section 3.7.3 and those points will not be re-iterated here. It is worth mentioning that, despite the considerable variation in average speed at which spasticity was assessed (section 4.3.1, table 4.2[a]), there were no significant differences within or between the two groups over the four assessment points.

Since the start of this study, guidelines were published re. the application of surface EMG (SENIAM project), detailing more precisely the optimum location for sensor placement It is expected that these will reduce the variation involved in electrode placement in future studies.

A further source of error emerged from the data in this study, which was thought to be associated with the positioning of the electrogoniometer. As explained in Chapter Two (section 2.3.3.2), one end block was strapped onto the posterior margin of the ulna, whilst the other was attached to the dorsal side of the humerus. However, the elbow joint displacement data suggested that less than full ROM had been tested in some cases – notably in those with more severe elbow spasticity. This finding could be explained by several factors, including the handle on the cantilever arm (which reduced maximal flexion to some extent) and elbow contractures. However, these could not fully explain the data. An additional factor may have been a pronation deformation in some people, which would have distorted the alignment between the two goniometer end blocks and the registration of

movement between them. This misalignment would manifest itself as a reduction in maximum flexion-extension ROM. In future, this problem could be solved by standardising the positioning of the electrogoniometer with respect to the direction of joint movement instead of anatomical landmarks, but this might not be straightforward to implement reliably. Registering movement in two planes rather than in one, as in the current study, may also help to overcome the problem, but the algorithm for calculating RTPM would need to be amended accordingly to include the resultant vector. Further work is required to solve this problem in future work.

Stroke Impact Scale

With its 60 questions, the SIS is rather extensive and it is plausible that, when participants completed their questionnaire, attention may not have been maintained at the same level, which may have affected the responses. Two participants in the CG did not return all questionnaires, but the reasons for their non-response remains unclear. On some occasions, it emerged that a participant had omitted a question or completed one in a way that was clearly out of character. In cases where participants appeared to have missed or misinterpreted a question, they would be contacted to complete or verify their response.

It was emphasised to participants that the questionnaire was about their own view and not about that of their carers, friends or family. However, with the questionnaire being completed at home, there was no control over how the questionnaire was completed.

It also emerged that the sensitivity of the SIS is unequal across all domains: although each question is scored on a 5-point Likert scale, the number of questions per domain varies between four and 10. This implies that a 1-point change on an item in a four-item domain constitutes a change of 6.3% (e.g. the strength domain: SIS-1), whereas an identical change in a 10-item domain (e.g. the ADL domain: SIS-5) yields only a 2.5% change. Hence, in the interpretation of the SIS outcomes, one should take the sensitivity of each subscale into consideration.

Grip force

As indicated previously and highlighted in the calibration study in Appendix 3.5, the accuracy and precision of the Jamar dynamometer were insufficient for forces below

107.8 N (11 kgf). For a population with persistent and severely impaired grip force, this meant that the data could not be interpreted with confidence. Even for the only participant (P08) who managed to produce grip force above this level, the data varied considerably over the four points of assessment, questioning the reliability of this outcome measure.

Technical problems were also experienced with placing and stabilising the instrument in the hands of some participants. On some occasions, they did not have sufficient force in their wrist supinators to maintain the instrument in the required position. At other times, participants would try and compensate by extending their elbow joint. All of these compensatory movements may have confounded the results (see Richards and Palmiter-Thomas, 1996). In future work, a cast could be used to stabilise the position of the elbow and wrist. However, fixed deformities, common after a stroke (Edwards, 2002), might make this alternative less practicable.

Participants' views

It is acknowledged that subjective bias was inevitable in noting and selecting participants' comments, although an attempt was made to represent participants' views in a balanced and honest manner. However, the informal method used in this study was clearly lacking in rigour. A more formal qualitative methodology (e.g. through semi-structured interview) would have been appropriate to explore participants' views more systematically, but this was out with the scope of the study. Given the importance of user views, it is important that this avenue of research be further developed in future research, as it appears to have been hardly explored.

5.5 ETHICAL CONSIDERATIONS

Despite the obvious focus of the study, it was surprising to find that some participants articulated very few UL-related occupational issues on the COPM, which suggested that these were not considered as a priority. Especially in people who may already have come to terms with the fact that complete recovery was not a realistic option, this raises the question whether it is ethical to confront them with their deficits and (implicitly) offer hope for further normalisation.

This question is not straightforward; on one hand, opportunities for further rehabilitation after stroke are considered by many clinicians and patients to be insufficient. On the other hand, a relentless belief that all problems will disappear if only more treatment were provided, could mask the fact that people have not yet come to terms with their condition. In that case, counselling might be more beneficial than mere therapy, which could actually reinforce the quest for unrealistic goals and postpone the acceptance of loss. Without being able to provide a clear answer, it is important than clinicians carefully consider the appropriateness of further rehabilitation for each individual patient, being aware of the issues described above.

5.6 RECOMMENDATIONS FOR CLINICAL PRACTICE AND RESEARCH

As highlighted before, the current study was underpowered due to an insufficient number of patients meeting the eligibility criteria. Given the exploratory nature of the study, effect size was not calculated. The study will need to be replicated first with a larger sample, before any firm conclusions may be drawn. A sample size estimation for a future trial is included in Appendix 5.1. However, on the basis of the available data, the following preliminary recommendations may be made for clinical practice and research, which are summarised in Box 5.1.

5.6.1 STROKE REHABILITATION: BOTULINUM TOXIN TREATMENT

The clinical guidelines on the use of BTX-A in adults with a stroke (Barnes et al., 2001; Royal College of Physicians, 2002), recommend that BTX-A be part of a comprehensive treatment programme. Despite these recommendations, a considerable proportion of people treated with BTX-A were not provided with additional therapy around the time of the study. Resource limitations in the NHS[6] as well as insufficient understanding of the limited effects of BTX-A by some clinicians, responsible for the referrals, may all have played a role. The literature in section

[6] At the time of the study, the cost of the research therapist's time (at Superintendent Physiotherapist Level II) was estimated at around £300 per participant for the entire therapy programme.

3.2.2.2 showed clearly that BTX-A primarily reduces resistance to passive movement, but that there is no robust evidence to demonstrate that it also promotes upper limb function or activity, which are the more clinically relevant domains. The data from the control group in the present study support the guidelines, since the combination of BTX-A with a passive treatment modality yielded no benefits in terms of functional activity. In contrast, data from the experimental group suggested that BTX-A combined with an intensive, functional, task-specific practice programme may improve upper limb function, as well as ADL, in some participants. Based on this preliminary evidence, if the primary aim of BTX-A treatment is to enhance functional activity, the recommendation is that it should be accompanied by a functional skill acquisition programme – where appropriate.

In many ways, it was not surprising to find that an intensive, functional skill acquisition programme yielded more benefits than a passive intervention, combined with BTX-A; although actual evidence has been lacking in this case. The literature on skill acquisition also highlighted that skills do not simply arise; they need to be specifically trained for. However, what is probably less self-evident is the finding that these benefits were observed in people several years after stroke. It is interesting that the assumption of a so-called "plateau" in recovery after stroke is increasingly being questioned (e.g. van der Lee *et al.*, 1999; Bach-y-Rita, 2000; (Page *et al.* 2005). Following CIT, Miltner *et al.* (1999), even found improvements in a patient 17 years after stroke. Taub and Wolf (1997, cited by Bach-y-Rita 2000, p. 368), suggested that the apparent "plateau" in recovery could instead represent a lack of transfer between treatment and ADL. Rather than attributing the lack of progress to the patient's limited potential for recovery, perhaps clinicians should question whether their therapeutic input actually continues to engage patients in learning skills that are relevant and useful. Especially the study by Page *et al.* (2005), which showed considerable improvement in upper limb activity in patients considered to have reached a steady state, provides thought-provoking evidence that it is time to question the notion of a so-called "plateau".

Clinicians may be inclined to be concerned about adverse effects of training programmes after stroke, especially with regards to spasticity. The data from this study indicated that there were treatment-related adverse events, mainly fatigue and transient upper limb pain, but these were benign and would all seem to be

manageable through changing the treatment schedule to some extent. Additionally, the data showed that there were no adverse effects of the training on spasticity. Taken together, until more evidence is available, these preliminary data may serve to encourage clinicians to offer further rehabilitation to people in the chronic stage after stroke, for whom a functional training programme would be suitable and appropriate.

The literature review in section 1.3 indicated that many BTX-A studies included a physiotherapy and/ or occupational therapy "package", but the details were insufficient to enable the effects of individual modalities to be determined. As many authors have emphasised, it is time that the "black box of therapy" (Ballinger *et al.*, 1999, Pomeroy and Tallis, 2002[b]) be unpacked so that the benefits of individual treatment strategies may be determined. Therefore, the recommendation is that further research be undertaken to compare and contrast the effects of other treatment modalities, administered together with BTX-A (e.g. functional electrical stimulation, constraint-induced therapy, robot-assisted training and virtual reality-mediated training) with different categories of patients. This information may assist in the development of predictive models for clinical practice, since at present there is insufficient information to be able to predict accurately which patients are more likely to benefit from which type of therapeutic input. In this study, the very small sample size and large number of potential covariates did not enable any predictions to be made. Rousseaux *et al.* (2002) suggested that the level of distal control and baseline level of spasticity in forearm muscles could be possible predictors for improved function following BTX-A. Other factors, e.g. somatosensory characteristics, visuo-spatial neglect, cognitive function, level of self-efficacy, aspects of self-perception and health beliefs may all be important factors in determining treatment outcome and these need to be investigated further.

5.6.2 STROKE REHABILITATION: SKILL ACQUISITION

As discussed in section 1.5, there is a dearth of research in the domain of skill acquisition following a brain lesion. It is unclear what the implications of contralateral neglect, cognitive or communication impairments are for the re-acquisition of functional skills. Since these problems are common in people with

stroke, research on skill acquisition in neurological rehabilitation would need to incorporate the expertise from different disciplines, including physiotherapists, occupational therapists, psychologists and movement scientists.

The current study employed a combination of physical and mental practice. Clearly, further work is now required to evaluate the effects of different physical and mental practice schedules. In this study, mental practice was integrated with physical practice to enhance carry-over into ADL, but it was also suggested that in the cognitive stage of learning, and/ or for those with cognitive deficits, it could be more effective to provide mental practice in separate sessions initially.

To enhance our understanding of the effects of mental practice, it would be of interest to assess the immediate (i.e. within a therapy session), as well as delayed effects on performance. Further research is also needed to determine the specificity of mental practice, i.e. whether it is task-specific or perhaps a more generic skill that could facilitate the acquisition of other categories of skills.

Neuro-imaging technology would be useful to explore brain activity associated with different strategies of mental practice and to further our understanding of any short-term and long-term neuroplastic changes that may occur as a result. This technology would also enable the effects of different brain lesions on the ability to engage in mental practice to be explored further.

5.6.3 OUTCOME ASSESSMENT: STANDARD VERSUS PATIENT-CENTRED MEASURES

The lack of congruency between changes in the ARAT and the COPM is worth some elaboration: the period between baseline and Week 4 shows a noteworthy discrepancy in the EG (table 4.7): the median change in the COPM-P signalled an improvement of approximately 33% (i.e. 3 points, range 1.5 to 5.0 points), whereas that in the ARAT was a mere 2 points (range -2 to 9 points). This mismatch was, at least initially, quite surprising. After all, the ARAT is portrayed as a functional measure and the COPM analysis only pertained to UL-related activities. However, when comparing the content of the two scales, a lack of overlap emerged. Whereas all ARAT tasks (bar one) are unimanual, many of the COPM activities required bilateral involvement (table 4.3). Further, whereas all ARAT activities are carried out straight in front of the person and on their ipsilateral side, many of the COPM

activities would probably occupy a larger part of user-centred space and, on occasions, cross midline. Also, all ARAT tasks are performed in sitting, whereas the COPM activities might additionally be carried out in standing or in transit. Finally, the ecological validity of some of the ARAT items (e.g. blocks, tubes) could be questioned. An attempt to visualise the relationships between the normal UL function domain, that of a person with severely limited arm function following a stroke, their general occupational performance domain and that occupied by the ARAT, as it emerged from the current study, has been made in fig. 5.1. It highlights the narrow focus of the ARAT, in comparison with the broader scope - but restricted sophistication - of the patient's UL function domain. (In fact, most of the ARAT tasks were quite literally out of reach for most participants.) Moreover, it shows that the participant's UL function domain only occupied a small part of their general occupational performance domain – which may explain the finding that not everyone in this study appeared to be primarily concerned with their affected arm.

The lack of correlation between the ARAT and COPM lends further support the statement by other authors, namely that the COPM yields information that cannot be obtained from standard outcome measures (Cup *et al.*, 2003). In conclusion, the implication for clinical practice and research is that a patient-centred outcome measure should be included routinely, as it adds a phenomenological dimension to an otherwise standardised set of outcomes, placing the findings within the unique context of each individual.

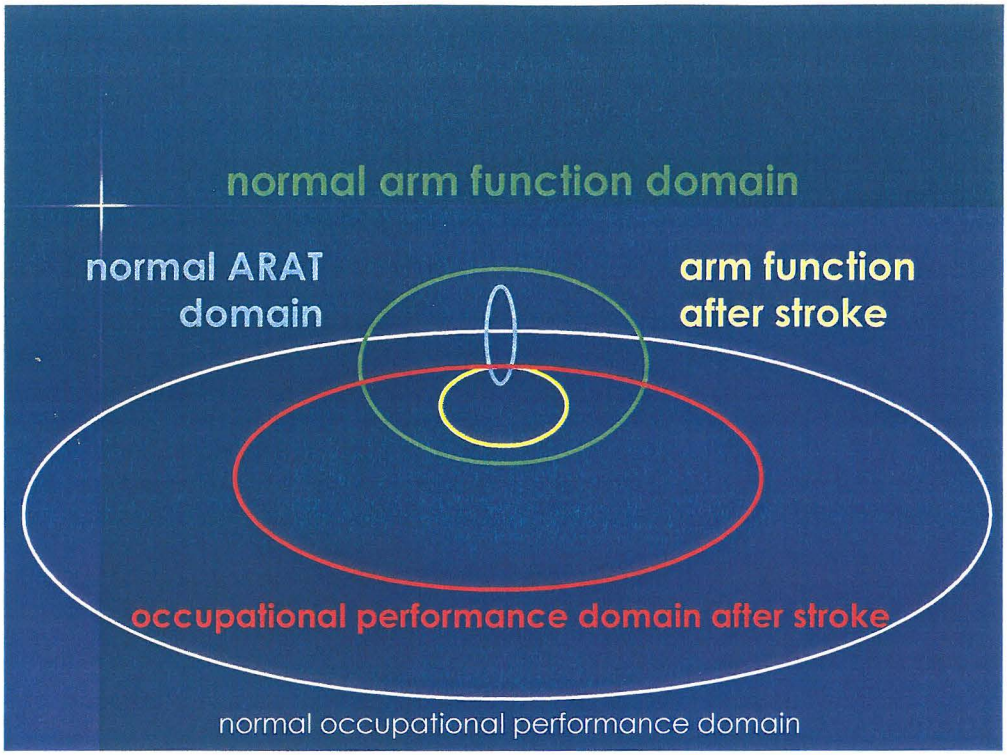


Figure 5.1
Venn diagrams representing a schematic relationship between the following domains: normal arm function (green), normal arm function as represented by the ARAT (blue) and occupational performance (white), as well as the arm function (yellow) and occupational performance (red) as they may be affected after stroke.
See text for details

Box 5.1
Summary of the main recommendations for clinical practice and research
BTX-A: botulinum toxin type-A. ICF: International Classification of Functioning, Disability and Health (2001), ARAT: Action Research Arm Test, COPM: Canadian Occupational Performance Measure.

Stroke Rehabilitation: research on UL spasticity management using BTX-A
- Replicate current study in multi-centre trial, with sufficiently large sample that is more representative of the stroke population
- Conduct further research into effects of other therapies (e.g. functional electrical stimulation, robot-assisted training, splinting), provided alongside BTX-A
- Include all three ICF domains in outcome assessment. The toolkit could consist of:
  - EMG (to measure spasticity)
  - ARAT (to measure activity limitation)
  - Motor Activity Log (as a more ecological measure of activity limitation), coupled with accelerometry of the affected upper limb
- Using qualitative research, explore the views of service-users on treatment needs.
- Include a patient-centred outcome measure in addition to standard outcome measures

Stroke Rehabilitation: audit spasticity management using BTX-A
- Carry out needs assessment of people requiring BTX-A for UL spasticity
- Audit the implementation of the BTX-A guidelines for the management of adult spasticity

Stroke Rehabilitation: clinical UL spasticity management using BTX-A
- Until further evidence is available and where appropriate, offer patients who have been injected with BTX-A, who have at least minimal hand function, a functional skill acquisition programme together with BTX-A treatment to enhance functional carry-over.

Stroke Rehabilitation – research on skill acquisition
- Study effects of the skill acquisition programme in a sub-acute stroke population
- Conduct further research into the efficacy of different proportions of physical and mental practice within a treatment session
- Conduct further research into the efficacy of different schedules of physical and mental practice within a treatment session
- Conduct further research into the immediate effects of mental practice on performance
- Study effects of cognitive and speech and language impairments, as well as contralateral neglect on skill acquisition involving the UL

5.7 SUMMARY AND CONCLUSIONS

The primary aim of the feasibility RCT, reported in Chapters Three to Five, was to investigate whether an additional skill acquisition programme, administered after BTX-A, would have any differential effects on upper limb spasticity or functional activity in people more than six months after stroke. The primary outcome measures were: arm function, assessed on a standard test (i.e. ARAT) and a patient-centred outcome measure (i.e. the COPM), as well as elbow flexor spasticity (surface EMG). The secondary outcomes were: resistance to passive movement

(RTPM, AS), grip force of the affected hand (GF) and relevant items from the Stroke Impact Scale (i.e. hand function, ADL and participation).

Both the experimental and the control group took part in a therapy programme for one hour per day, five days per week, for a total of three weeks, commencing between four and five days after injection with BTX-A into spastic UL muscles. A single physiotherapist delivered all the interventions, while a blinded assessor evaluated all outcomes (except for the COPM, which was evaluated by the physiotherapist). At the start of each session, all participants were given a 15-minute standardised stretching programme to elongate the muscle groups affected by spasticity. The experimental group (EG) then took part in a 45-minute evidence - and theory-based functional skill acquisition programme, using a standardised protocol with combination of physical and mental practice. In contrast, those in the CG were fitted with an inflatable upper limb pressure splint around their affected arm and rested for the remainder of their session.

Participants returned for follow-up assessment immediately after the completion of the therapy programme (Week 4), midway through the BTX-A cycle (Week 7) and at the end of this cycle, prior to re-injection (Week 13).

A total of 14 participants were recruited and randomised, using permuted block randomisation, to either the EG (n=7) or the CG (n=7). On average, both groups were severely impaired in all aspects of upper limb function. There were no differences between any of the dependent variables at baseline. Two participants dropped out from the EG before the end of the first week, due to factors unrelated to the content of the treatment. There was no drop-out from the CG. Attendance in both groups was around 90%.

Due to the small sample size, statistical techniques were used only to explore the data and their results should therefore be interpreted with due caution. Given the nature of this study, the effect size was not calculated. Although it is not possible to state the statistical significance of the results with confidence, it was possible to comment on their clinical relevance on a case-by-case basis.

The results showed that, in terms of upper limb activity assessed on a standard measure (i.e. the ARAT), the EG demonstrated a significantly greater improvement on the ARAT than the CG ($p=0.003$) in the period between baseline and Week 7 - i.e. three weeks after completion of the therapy programme. Three out of five

participants in the EG achieved or exceeded the minimal clinically important difference (i.e. 6 points) at some stage during the study, whilst changes in the CG were negligible throughout. There were no other significant differences in changes in ARAT between the two groups over any of the other study phases.

In terms of changes in self-selected UL-related occupational issues (COPM), there were no statistically significant differences between the two groups over any of the other study phases in the performance or the satisfaction dimensions of this measure. However, in clinical terms, there were greater improvements in self-rated performance (COPM-P) between baseline and Week 4 in the EG than in the CG ($p=0.06$). Satisfaction scores improved in both groups, reaching a higher level in the EG than in the CG at the end of the study.

With regards to grip force of the affected hand, this was consistently below the threshold at which the instrument was capable of registering accurately and precisely. For this reason, the data could not be interpreted in a meaningful way.

In terms of changes in self-reported hand function (SIS-7), the EG showed more improvement than the CG between baseline and Week 4 ($p=0.04$), although this differential change did not reach the critical p-value. This finding would appear to contradict the changes on the ARAT, which showed no difference between the two groups over this period. This discrepancy was explained by the difference in specificity, with the stroke-specific scale (SIS) being more responsive than the generic scale (ARAT).

Perhaps the most surprising finding was that the EG also reported more improvement in terms of self-reported ADL (SIS-5) than did the CG between start and end of the study ($p=0.02$) - although this result failed to reach the critical p-value. This finding was unexpected because it occurred nine weeks after the end of the therapy programme and at a stage where the level of UL spasticity would have returned to baseline in most cases. Furthermore, these findings contrasted with the literature, which had shown insufficient evidence of UL exercise having a beneficial effect on ADL (Logigian *et al.,* 1983; Jongbloed *et al.,* 1989; Kwakkel *et al.,* 1999; Lincoln *et al.,* 1999; Sunderland *et al.,* 1992; Gelber *et al.,* 1995; Werner *et al.,*

1996; Feys *et al.,* 1998; Rodgers *et al.,* 2003). However, the findings supported those reported by Steultjens *et al.* (2003), who found significant improvements in ADL following specific skills training strategies. Taken together, these findings highlight the importance of occupationally embedded training, as opposed to mere exercise to enhance functional carry-over.

With regards to participation (SIS-8), there were no significant differences between the two groups over any of the study periods. All in all, there was a lack of impact on this dependent variable in either study group.

In terms of RTPM and spasticity, there were no significant differences between the two groups in terms of clinically (i.e. AS) or biomechanically assessed resistance to passive elbow extension. There were also no significant differences between the two groups in terms of elbow flexor EMG. Furthermore, there were no adverse effects of the skill acquisition intervention on spasticity.

In terms of adverse events, fatigue and transient UL pain were most commonly reported in both groups. There were no serious treatment-related events.

Clearly, the improvements in the EG need to be placed in the context of the level of impairment at the start of the study, which was generally severe and in absolute terms, improvements were small. This finding highlights the need for more effective rehabilitation input for the affected upper limb in the subacute stage after stroke in order to prevent - as much as possible - the persistent, severe arm impairments found in this study cohort.

In terms of assessment, comparing the results from the different outcome measures highlighted the need to include all three domains of the WHO ICF (2003) as well as a patient-centred outcome measure. Although the impact of the intervention programme on participation restrictions was under-explored in this study (as only a section of the SIS addresses this issue), the data collected so far clearly call for further research. Furthermore, comparing assessor-administered with self-report measures was interesting. The content and ecological validity of the ARAT came under scrutiny when discrepancies were found between scores on the ARAT on the

one hand and the scores on the COPM and SIS on the other hand. This revealed that the ARAT was restricted to a very narrow domain of upper limb function, yielding a poor representation of UL activities that are typically undertaken by people in the chronic stage after stroke. Finally, the patient-centred outcome measure (COPM) added a unique and invaluable dimension to the otherwise standard set of measures.

When placing the evidence of this feasibility RCT against the guidelines from the National Institute for Health and Clinical Excellence (NICE, 2001), it can be seen that evidence arrives at level "Ib" (i.e. at least one RCT) and the corresponding grade of recommendation would be "A". However, as highlighted earlier, the study first needs to be replicated with a sufficiently powered sample. Meanwhile, it is hoped that these preliminary findings may encourage clinicians to consider providing people, who require BTX-A treatment for chronic UL spasticity following a stroke, with an opportunity to engage in additional functional skill training where appropriate, until further evidence has been published.

CHAPTER SIX

SYNOPSIS AND REACHING FORWARD: IMPROVING EVIDENCE- AND THEORY- BASED STROKE REHABILITATION

6.1 INTRODUCTION

This thesis focused on a specific domain within stroke rehabilitation, i.e. functional activity involving the affected upper limb in people with chronic spasticity. What may the implications of this particular domain be for stroke rehabilitation in general? Directing the spotlight onto spasticity and functional activity exposed a number of questions related to evidence- and theory-based practice that reflect broader issues in current neurological rehabilitation. These comprised: how are neurological impairments and activity limitations defined and measured? What may the benefit of continuing rehabilitation be for people who have reached a "plateau" after stroke? How do we know what the therapeutic input comprises? What is the scientific robustness of the tools, used to assess outcomes? What are the views of the service user on any treatment effects? How may rehabilitation enhance long-term, functional activity? These questions will be addressed in the following sections.

6.2 SPASTICITY: 2½ DEFINITIONS

"Spasticity" is only one of the frequently observed phenomena in neurological rehabilitation. Despite its high prevalence, Chapter Two exposed the considerable lack of agreement on the interpretation of this concept. It was argued that this was not only a matter of academic, but especially of clinical concern, as it is crucial to be

clear on the nature of the problem being treated before effective intervention can be instigated. One interpretation in the literature (i.e. Lance, 1980) characterises spasticity as a single impairment within the upper motor neuron (UMN) syndrome, whilst according to a second interpretation (see Edwards, 2002), spasticity encompasses the entire UMN syndrome. The review of spasticity measurement techniques in Chapter Two yielded numerous other interpretations, which could all be placed along a continuum in between these two extremes. The cause of the confusion regarding this concept was identified as a category mistake and it was suggested that categorising spasticity as an umbrella term for all active, positive symptoms of the UMN syndrome, would overcome this problem and provide a way forward for more clinically relevant research in this domain. Thus, a new definition of spasticity was proposed by the SPASM consortium, i.e.:

> *"Disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles"* (Pandyan *et al.* 2005: p. 5)

In actual fact, this proposition provides a working definition, as the challenge for those accepting it will be to define precisely which aspect of spasticity is being dealt with. The identification of the behavioural and neurophysiological signatures of the various components of spasticity will require considerable research effort in future. Work undertaken by Sanger and his group (2003) in the area of paediatric neurology provides an example of how this classification may take shape and it is the intention that his group and the SPASM consortium collaborate and move this issue forward.
It is important to note that the proposed definition only includes neurogenic factors contributing to resistance to passive movement but excludes non-neurogenic factors (e.g. contractures). Accordingly, one recommendation put forward is that a valid spasticity measurement system should include a measure of reflex- or muscle activity.

Interestingly, it became apparent from the systematic review in section 1.3 that most of the evidence pertaining to the effects of botulinum toxin Type A (BTX-A) on upper limb spasticity in stroke is based on the (modified) Ashworth Scale, which fails to differentiate between neurogenic and non-neurogenic contributions to RTPM. It was therefore concluded that the effect of BTX-A on actual spasticity, defined as per the proposed definition (or by Lance's (1980) definition) is largely unknown. Given the

increasing enthusiasm for BTX-A in spasticity management, it will be necessary to improve outcome measurement in this domain in order to justify the increase in treatment costs[1].

Based on the new definition, a second recommendation was put forward, namely to update the predominant model underpinning traditional spasticity assessment. This may be characterised as a passive perturbation paradigm and forms the basis for the majority of complex biomechanical and neurophysiological methods as well as commonly used clinical tests. Fellows *et al.* (1994) suggested that testing spasticity according to this paradigm provides little information about difficulties encountered during functional activity. Placed in the context of the model by Shumway-Cook and Woollacott (1995), which describes motor control as emerging from the individual, the task and the environment, it emerges that traditional spasticity measurement has concentrated on the individual but neglected the environment as well as the task, which - ironically – tended to require the patient to shut down all activity. Having defined spasticity as a collection of sensorimotor control problems, it follows that its assessment should encompass the entire continuum of motor function; from passive motion (as per traditional model) to purposeful activity. Equally, the role of sensory input should be studied systematically and to this effect, robotics and virtual environments could be employed (e.g. the GENTLE/S project http://www.gentle.reading.ac.uk/). In contrast to the traditional laboratory environment, studies should also explore the effects of more ecological environments on sensori-motor control as only these will give insight into the problems that patients experience in real-life situations. Figure 6.1 illustrates how spasticity could be conceptualised within the (adapted) model by Shumway-Cook and Woollacott (1995).

Taken together, the main lesson learned from placing the spotlight onto spasticity (which is, as mentioned above, just one of the frequently observed impairments in neurological rehabilitation) was that despite its familiarity, this concept was far from

[1] A multicentre RCT is underway at the time of writing to establish the clinical affects and cost-effectiveness of BTX-A in upper limb spasticity management following stroke in the UK, led by Dr. H. Rodgers: [http://www.ncchta.org/projectdata/1_project_record_notpublished.asp?PjtId=1408&SearchText=You+Selected++AND++AND+] (van Wijck et al., 2006[b])

unambiguous. It required an interdisciplinary debate to clarify its interpretation and put forward recommendations for improving the methods whereby it may be measured.

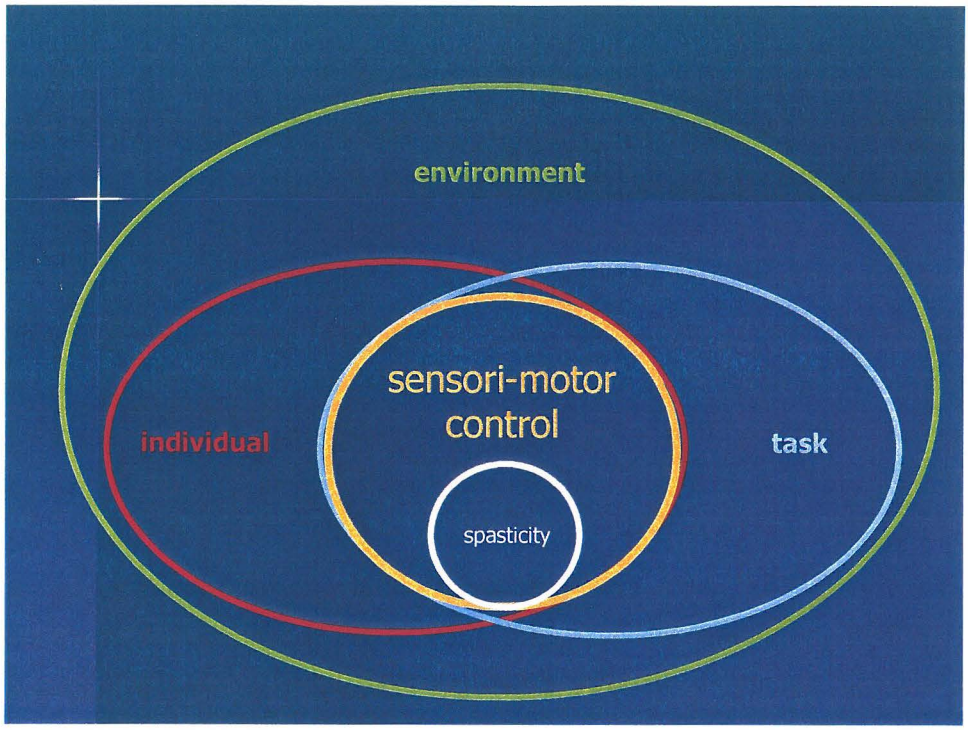


Figure 6.1
Model for interpreting spasticity within the context of the (adapted) general model of motor control published by Shumway-Cook and Woollacott (1995)
See text for details

6.3 REVISITING THE NOTION OF A "PLATEAU" AFTER STROKE

The commonly held assumption of a "plateau" in recovery after stroke was called into question in Chapter One. The findings from the feasibility RCT (Chapters Three to Five), further challenged this assumption. Bach-y-Rita (2000) emphasised that the potential for brain reorganisation after a CNS lesion may still be present for many years after injury and that specific rehabilitation input in the chronic stage is necessary to realise this potential. Therefore, in order to be able to address the needs of people after stroke, it is important to highlight to clinicians, health care

funders as well as patients and their carers that improvements in functional activity may still be possible, even several years after the acute event.

6.4 INTERVENTION

6.4.1 SPECIFYING THE INPUT

In order to be able to replicate any study evaluating the efficacy of a therapeutic intervention, sufficient detail pertaining to the actual input is required. Describing interventions on the basis of traditional "approaches" has been shown to be insufficient (Pollock *et al.,* 2003). In order to improve current knowledge and understanding with regards to the input-output relationship in neurological rehabilitation, it is necessary improve the specification of therapeutic input (e.g. DeJong *et al.* 2004; Pomeroy and Tallis, 2002a; Kwakkel, 1999). Although it is acknowledged that every patient is unique, it may nevertheless be possible to identify at least the core principles of treatment (e.g. type, number and duration of activities) as a basis for the intervention for specific subgroups of patients. A number of initiatives, presented in section 1.5, have been reported in the literature, e.g. Constraint Induced Therapy, Bilateral Isokinematic Training and Arm Ability Training. The RCT described in Chapters Three to Five suggested a protocol for a specific group of people, which was based on current theories and evidence.

With an ageing population and government initiatives to promote better care in the community, there is an increasing need to develop a portfolio of interventions that can be "packaged" into home-based activity programmes, while embracing opportunities for tele-medicine applications (e.g. Gourlay *et al.,* 2000; Piron *et al.,* 2004; Adamovich et al., 2005; Holden, 2005). These programmes would provide people, living in the community, with an opportunity to engage in self-paced, independent but supervised practice in their own home environment. This could provide a more efficient and cost-effective way to manage care in the community than the present service model in the UK with its emphasis on outpatient-based, one-to-one interventions.

6.4.2 ENHANCING LONG-TERM FUNCTIONAL ACTIVITY

Before long-term functional benefits of spasticity management can be improved, the role of spasticity in activity needs to be better understood. The literature in sections 1.3 and 1.4 showed that, at the time of writing, surprisingly little was known about the relation between spasticity and activity.

Potentially, there are at least three different avenues of research that could elucidate the relationship between spasticity and activity, namely by investigating: 1) the effects of treating spasticity on activity limitations, 2) the effects of treating activity limitations on spasticity and 3) factors involved in sensori-motor control, affecting both spasticity and activity.

The first avenue was investigated by Platz *et al.* (2005), who indicated that this question was poorly researched, while van Kuijck *et al.* (2002) concluded that functional effects of pharmacological spasticity agents tended to be absent or limited.

Currently, the second line of research also yields little useful information, but there is growing evidence (including from the RCT described in Chapters Three to Five in this thesis) that increasing activity is unlikely to have a detrimental effect on spasticity (Badics *et al.,* 2002; Bourbonnais *et al.,* 2002; Bütefisch *et al.,* 1995; Morris *et al.,* 2004). More systematic and fine-grained research is necessary to compare and contrast different forms of training, but these initial findings are promising.

Evidence from the third line of research will require a thorough review of the literature, but the first impression is that the data from motor control studies have limited external validity, with tasks typically employed bearing little resemblance to ADL. However, several interesting motor control studies have been published, which have challenged commonly held beliefs. In their ground-breaking study, Gowland *et al.* (1992) showed that paresis in the agonists of the upper limb in stroke patients was more closely associated with activity limitations than abnormal activity in the antagonists. This evidence overturned the then commonly held belief that spasticity of antagonist muscles was the key barrier to normal movement (Bobath,

1969). The importance of the role of spasticity in active movement was further called into question by thought-provoking results from a study by Fellows *et al.* (1994). This indicated that abnormal EMG, found in upper limb antagonist muscles during an unloaded upper limb movement task, disappeared when the same task was performed against a load. Other studies provided contradictory results regarding the relationship between spasticity and active function (Lin *et al.,* 1999; and O'Dwyer *et al.,* 1996). Studies by Levin (1996 and Cirstea *et al.,* 2000) suggested that spasticity was associated with abnormal synergies or compensatory movements, which could adversely affect function, but Levin (1996) concluded that clinical spasticity scores provided little information about the nature of the motor control problems.

Taken together, it is clear that there is a lack of understanding regarding the relationship between spasticity and activity and that an extended paradigm, where spasticity is investigated *during* functional activity needs to be developed.

In general, with regards to the long-term functional benefit of physiotherapeutic interventions (section 1.5), the evidence for many strategies was inconclusive, which was attributed to methodological problems in many cases. Despite these weaknesses, the evidence clearly indicated that interventions yielding the best functional outcomes were characterised by task-specific practice of functional activities, with ample opportunity for practice.

However, a dearth of literature emerged concerning optimal strategies for structuring the practice process. Fuhrer and Keith (1998) were of the opinion that therapists in neurological rehabilitation tended to structure the learning process more on the basis of intuition rather than evidence. Additionally, it became apparent that physiotherapists tend to concentrate on overt learning, leaving potentially beneficial covert strategies, such as mental practice and observational learning, largely unexplored.

In conclusion, the main recommendations from Chapter One were that treatment, aimed at improving functional carry-over, should include plentiful practice of specific

activities that are meaningful for the individual. The need to conduct more research into optimum skill acquisition strategies following stroke was also highlighted.

Given the lack of research within the stroke literature on optimal skill acquisition processes, the literature on neuroplasticity and motor learning in the general population was consulted in section 1.6. Studies on neuroplasticity in primates following experimental brain lesions suggested that long-term functional carry-over is not achieved through the repetition of mere movement, but through meaningful, purposeful activity instead. Bach-y-Rita (2000) argued, on the basis of neuro-imaging studies with primates, that rote exercise was "virtually useless" (p. 369), which was substantiated by the evidence from some of the studies described in section 1.5 (e.g. Bourbonnais *et al.,* 2002; Turton and Butler, 2004). This may be understood from a neural network model of the brain: compared to sheer repetitive limb movement, the task of solving functional problems may require perceptual, cognitive, linguistic and executive processes, which would be expected to activate more extensive and distributed neural networks, depending on the task. Additionally, research has indicated that different forms of practice of a particular task, ranging from overt to covert, activate overlapping neural networks (Jeannerod, 2005), which lends support for the instigation of covert learning strategies in skill acquisition. Especially given the restricted opportunity to engage in structured practice in most rehabilitation settings (Esmonde *et al.,* 1997), task-specific covert practice should be employed where appropriate to supplement the learning process. Evidence from studies on skill acquisition in non-impaired people provided robust evidence that, although intuitive strategies (e.g. manual guidance, blocked practice and ample feedback) may serve to improve short-term performance, they often fail to enhance long-term learning – the actual aim of rehabilitation. This is a particular concern, given the view of Fuhrer and Keith (1998) that therapists use intuition rather than evidence to structure the rehabilitation process. It is possible that the lack of carry-over, even from one therapy session to the next, identified by Taub and Wolf (1997), may be partially attributable to rehabilitation focusing on performance instead of learning.

However, one should be cautious with respect to applying motor learning strategies that have been shown to be effective in non-impaired populations to neurological rehabilitation, without questioning their validity. Taken together, there is an urgent

need to undertake further research into optimal skill acquisition strategies in neurological rehabilitation in order to address the current problem of limited carry-over into useful activity.

6.5 MEASURING THE OUTPUT

6.5.1 THE PATIENT'S PERSPECTIVE

Evaluating the BTX-A literature (section 1.3) and the literature on physiotherapy rehabilitation (section 1.5) revealed a striking omission in the majority of studies, i.e. the patient's perspective. In the physiotherapy literature, there was little indication that patients had been involved in the goal setting process and very little evidence that their opinion on treatment effects had been sought. In the literature on BTX-A, a handful of studies had involved the patient in selecting treatment goals and/ or scoring their progress, but the usage of validated outcome measures was poor.

As a result, little is known about the relevance of certain aspects of stroke rehabilitation to the service users, a situation which requires urgent improvement, since several studies have shown that patient centred outcome measures yield information that cannot be obtained through any of the standard outcome measures (Cup *et al.* 2003, Lai *et al.,* 2002). The results from the RCT, presented in Chapter Four, lend further support to this idea. The Chartered Society of Physiotherapy-specific Guidelines for Stroke (2002), based on the Royal College of Physician's guidelines (2004), stipulate that the patient should be involved in goal setting and that goal attainment scaling may be useful. However, based on experience, this guideline did not appear to be part of routine clinical practice at the time of writing and further research will be necessary to identify the barriers to this.

Including an inductive approach to exploring patients' opinions in efficacy research may foster the generation of new hypotheses, which in turn may be tested using a deductive approach. This combined methodology will foster innovation in neurological rehabilitation and ensure that efficacy research in rehabilitation addresses issues considered to be relevant by those who use the service.

6.5.2 STANDARD OUTCOME MEASURES

Since patient-centred outcome measures are in principle not norm-referenced, it is also important to include standard measures. The current trend in neurological rehabilitation to include all three domains of the WHO ICF (2001) in standard outcome measures is a welcome attempt to generate a more comprehensive, biopsychosocial picture of a patient's issues. However, it needs to be acknowledged that the physiotherapy literature is still predominantly impairment-orientated, which is evident from the reviews in sections 1.3-1.5. Initiatives in multidisciplinary research and inter-professional education are expected to improve this situation in future.

6.5.3 INTEGRATING CLINICAL ASSESSMENT WITH MEASUREMENT TECHNOLOGY

Outcome assessment in neurological rehabilitation depends largely on ordinal level scales, many of which are hampered by methodological limitations which could be overcome by using technology judiciously. A survey by van Wijck *et al.* (2001) showed that quantitative outcome measures are still relatively uncommon in neurological rehabilitation, despite tremendous advances in movement measurement technology. As a result, Work at the Centre for Rehabilitation and Engineering Studies at the University of Newcastle upon Tyne concentrates on developing methods whereby measurement technology can be integrated with routine clinical assessment in order to obtain data that can be interpreted clinically but that benefit from the strengths of using measurement technology (Pandyan *et al.*, 2002c). The resulting data are used to develop better models of specific impairments, which in turn are used to inform clinical practice and assess its effects.

Taken together, outcome assessment in neurological rehabilitation may be improved in the following ways, namely by: 1) including a patient-centred outcome measure, 2) including the three pillars of the ICF where this is meaningful, and 3) integrating sensible measurement technology with clinical assessment, where relevant.

6.6 CONCLUSIONS

The main recommendations for improving stroke rehabilitation, formulated throughout this chapter, can only be achieved through better collaboration between patients/ study participants, clinicians, engineers and scientists. New therapeutic developments are likely to arise from interdisciplinary collaborations, e.g. between various health care professions, engineering and neuroscience, embracing the opportunities offered by emerging technologies whilst ensuring they meet patient needs and are feasible in clinical practice. As far as evidence-based practice is concerned, physiotherapy is a new discipline and many therapeutic procedures are not yet supported by research (Partridge, 2002). However, rather than "evidence of absence" of therapeutic effects, this is more reflective of "absence of evidence", due to a paucity of information. One way of addressing this problem is by improving assessment tools. Improved quality of information will foster the development of more robust models of impairments and activity limitations, which in turn will enhance knowledge, understanding and clinical practice, the effects of which will be evaluated though ever improving assessment tools. This primarily deductive process should be accompanied by an inductive process, seeking the opinions of patients/ study participants and their carers on the outcomes and processes of the health technologies they experience. Thus, the frequently encountered schisms between clinical practice, research and the patient's experience may be begin to dissolve and develop into a more integrated, patient-centred, evidence and theory-based approach to stroke rehabilitation.

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LIST OF APPENDICES

* Appendices 1-5 may be found on the CD-ROM accompanying this thesis

APPENDIX 6

PHD-RELATED PUBLICATIONS

PEER-REVIEWED JOURNAL PUBLICATIONS

1 PANDYAN, A.D., VAN WIJCK, F.M., STARK, S., VUADENS, P., JOHNSON, G.R. & BARNES, M.P. (2006) The construct validity of a spasticity measurement device for clinical practice: An alternative to the Ashworth scales. *Disability and Rehabilitation,* 28, 579-85.

2 PANDYAN, A.D., COUSINS, E., VAN WIJCK, F., BARNES, M.P.& JOHNSON, G.R. Spasticity research: some common catches (2005) *Archives of Physical Medicine and Rehabilitation,* 86: 845

3 PLATZ, T., PINKOWSKI, C., VAN WIJCK, F., KIM, I-H., DI BELLA, P. & JOHNSON, G. (2005) Reliability and validity of arm function assessment with standardised guidelines for the Fugl-Meyer Test, Action Research Arm test and Box and Blocks Test: a multi-centre study. *Clinical Rehabilitation,* 19, 452-62.

4 PANDYAN, A.D., JOHNSON, G.R., GREGORIC, M., WOOD, D., VAN WIJCK, F., BURRIDGE, J., PLATZ, T., HERMENS, H.& VOERMAN, G. (2005) Spasticity: Clinical perceptions, neurological realities and meaningful measurement. *Disability and Rehabilitation,* 27, 2-6.

5 WOOD, D.E., BURRIDGE, J.H., VAN WIJCK, .FM.J., MCFADDEN , C., HITCHCOCK, R.A., PANDYAN, A.D., HAUGH, A., SALAZAR-TORRES, J.J. & SWAIN, I.D. (2005). Biomechanical approaches applied to the lower and upper limb for the measurement of spasticity: a systematic review of the literature. *Disability and Rehabilitation,* 27, 19-32.

6 BURRIDGE, J.H., WOOD, D.E., HERMENS, H.J., VOERMAN, G.E., JOHNSON, G.R., VAN WIJCK, F., PLATZ, T., GREGORIC, M. & HITCHCOCK, R. (2005). Measurement of spasticity: recommendations for clinical and research applications. *Disability and Rehabilitation,* 27, 69-80.

7 PANDYAN,A.D., VUADENS, P., VAN WIJCK, F.M.J., STARK, S., JOHNSON, G.R. & BARNES, M.P. (2002). Are we underestimating the clinical efficacy of Botulinum Toxin (Type A)? Quantifying changes in elbow spasticity and strength, and upper limb function following treatment in a unilateral post stroke population. *Clinical Rehabilitation,*16, 656-60.

8 VAN WIJCK, F.M.J., PANDYAN, A.D., JOHNSON G.R. & BARNES, M.P. (2001) Assessing motor deficits in neurological rehabilitation: patterns of instrument usage. *Neurorehabilitation and Neural Repair,* 15, 23-30.

CONFERENCE ABSTRACTS

9 VAN WIJCK, F., MACKENZIE, J., PANDYAN, A.D., BARNES, M.P. & JOHNSON, G. (2006[a]) Improving functional activity of the spastic upper limb in the chronic stage after stroke following botulinum toxin. *Neurorehabilitation and Neural Repair*, 20, 173. *World Congress for NeuroRehabilitation,* 12-16 February 2006, Hong Kong.

10 VAN WIJCK, F., PRICE, C.I.M., BARNES, M.P., FORD, G.A. & RODGERS, H. (2006[b]) What is the clinical effect and cost effectiveness of treating upper limb spasticity due to stroke with botulinum toxin? *Neurorehabilitation and Neural Repair*, 20, 199-200. *World Congress for NeuroRehabilitation,* 12-16 February 2006, Hong Kong.

11 VAN WIJCK, F., MACKENZIE, J., HOOPER, J., PANDYAN, A.D., BARNES. M. & JOHNSON, G. (2005) Skill acquisition in stroke patients with chronic upper limb spasticity: combining botulinum toxin with task-orientated motor learning. *South African Society of Physiotherapy 2nd International Congress,* , 23-29 May 2005, Johannesburg, South Africa.

12 VAN WIJCK, F., MACKENZIE, J., HOOPER, J., PANDYAN, A.D., BARNES, M. & JOHNSON, G. (2004) Effects of botulinum toxin and motor learning on upper limb function in stroke patients with chronic spasticity: standardised versus patient-centred outcomes. *Spasticity: Evidence based measurement and treatment.* 9-11 December 2004, Newcastle upon Tyne.

13 PANDYAN, A.D., VAN WIJCK, F.M.J., STARK, S., VUADENS, P., JOHNSON, G.R. & BARNES, M.P. (2004) Measuring aspects of spasticity: a simple clinical approach to routine measurement. *Spasticity: Evidence based measurement and treatment.* 9-11 December 2004, Newcastle upon Tyne.

14 VAN WIJCK, F., MACKENZIE, J., HOOPER, J., BARNES, M.P. & JOHNSON, G.R. (2004) Improving arm function in patients with chronic spasticity: combining Botulinum toxin with a task-oriented motor learning programme. *International Journal of Rehabilitation Research,* 27, S1, 109.

15 BARNABY, B., VAN WIJCK, F.M.J. & PANDYAN, A.D. (2002) Ashworth score zero: normative data estimates for resistance to passive elbow extension obtained from a female non-impaired adult sample. *13th European Congress of Physical and Rehabilitation Medicine,* 28-31 May 2002, Brighton.

16 STARK, S., TINDALL, C.E., ATKIN, H.M., VAN WIJCK, F.M.J., ALEXANDER, S., BARNES, M.P. & PANDYAN, A.D. (2002) A retrospective study of upper limb problems and their associated interventions following neurological event. P. 191. *3rd World Congress in Neurological Rehabilitation* 2-6 April 2002, Venice, Italy,.

17 PANDYAN. A.D., VUADENS, P., VAN WIJCK, F.M.J., STARK, S., JOHNSON, G.R. & BARNES, M.P. (2002) A simple biomechanically based technique to measure spasticity in routine clinical practice - Results from a preliminary clinical trial. Pp. 195-196. *3rd World Congress in Neurological Rehabilitation* 2-6 April, 2002, Venice, Italy,.

18 VAN WIJCK, F.M.J., PANDYAN, A.D., JOHNSON, G.R. & BARNES, M.P. (2001) Assessing motor deficits in neurological rehabilitation: a profile of instrument usage. *Journal of the Neurological Sciences*, 187, S1: S184. *XVII World Congress of Neurology,* 17 - 22 June 2001, London,.

19 PANDYAN, A.D., VUADENS, P., VAN WIJCK, F.M.J., STARK, S., JOHNSON, G.R.& BARNES, M.P. (2001). Clinical efficacy of Botulinum toxin-Type A (Botox®) in a chronic stroke population: Paradoxical findings from objective measures of spasticity and strength. *Journal of the Neurological Sciences*, 187, S1: S217. *XVII World Congress of Neurology,* 17 - 22 June 2001, London,.

20 PANDYAN, A.D., VUADENS, P., VAN WIJCK, F.M.J., STARK, S., JOHNSON, G.R. & BARNES, M.P. (2001). Outcome measures for treatment with Botulinum Toxin Type A (Botox®) for elbow spasticity in a chronic post-stroke population. *1st World Congress of the International Society of Physical and Rehabilitation Medicine*, July 2001, Amsterdam, The Netherlands.

BOOK AND BOOK CHAPTERS

21 PLATZ, T., PINKOWSKI, C., VAN WIJCK, F. & JOHNSON, G.R. (2005) *ARM: Arm Rehabilitation Measurement. Manual for performance and scoring of the Fugl-Meyer test (arm section), Action Research Arm Test and the Box-and-Block Test.* Baden-Baden: Deutscher Wissenschafts-Verlag (DWV)

22 BAER, G.D. & VAN WIJCK, F.M.J. (2005). Physical therapy. In: BARNES, M.P., DOBKIN, B. & BOGOUSSLAVSKY, J. (Eds.). *Recovery after Stroke*. Cambridge: Cambridge University Press, 226-58

23 PANDYAN, A.D., VAN WIJCK, F.M.J.& JOHNSON, G.R. (2002). Instrumentation in experimentation. IN: GREENFIELD, T. (ED.). *Research Methods, Guidance for Postgraduates*, 226-35. London: Arnold